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Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

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Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

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[Intervention Review]

Balneotherapy (or spa therapy) for rheumatoid arthritis

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ABSTRACT

Background

No cure for rheumatoid arthritis (RA) is known at present, so treatment often focuses on management of symptoms such as pain, stiffness and mobility. Treatment options include pharmacological interventions, physical therapy treatments and balneotherapy. Balneotherapy is defined as bathing in natural mineral or thermal waters (e.g. mineral baths, sulphur baths, Dead Sea baths), using mudpacks or doing both. Despite its popularity, reported scientific evidence for the effectiveness or efficacy of balneotherapy is sparse. This review, which evaluates the effects of balneotherapy in patients with RA, is an update of a Cochrane review first published in 2003 and updated in 2008.

Objectives

To perform a systematic review on the benefits and harms of balneotherapy in patients with RA in terms of pain, improvement, disability, tender joints, swollen joints and adverse events.

Search methods

We searched the Cochrane 'Rehabilitation and Related Therapies' Field Register (to December 2014), the Cochrane Central Register of Controlled Trials (2014, Issue 1), MEDLINE (1950 to December 2014), EMBASE (1988 to December 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to December 2014), the Allied and Complementary Medicine Database (AMED) (1985 to December 2014), PsycINFO (1806 to December 2014) and the Physiotherapy Evidence Database (PEDro). We applied no language restrictions; however, studies not reported in English, Dutch, Danish, Swedish, Norwegian, German or French are awaiting assessment. We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing and recently completed trials.

Selection criteria

Studies were eligible if they were randomised controlled trials (RCTs) consisting of participants with definitive or classical RA as defined by the American Rheumatism Association (ARA) criteria of 1958, the ARA/American College of Rheumatology (ACR) criteria of 1988 or the ACR/European League Against Rheumatism (EULAR) criteria of 2010, or by studies using the criteria of Steinbrocker.

Balneotherapy had to be the intervention under study, and had to be compared with another intervention or with no intervention.

The World Health Organization (WHO) and the International League Against Rheumatism (ILAR) determined in 1992 a core set of eight endpoints in clinical trials concerning patients with RA. We considered pain, improvement, disability, tender joints, swollen joints and adverse events among the main outcome measures. We excluded studies when only laboratory variables were reported as outcome measures.

Data collection and analysis

Two review authors independently selected trials, performed data extraction and assessed risk of bias. We resolved disagreements by consensus and, if necessary, by third party adjudication.

Main results

This review includes two new studies and a total of nine studies involving 579 participants. Unfortunately, most studies showed an unclear risk of bias in most domains. Four out of nine studies did not contribute to the analysis, as they presented no data.

One study involving 45 participants with hand RA compared mudpacks versus placebo. We found no statistically significant differences in terms of pain on a 0 to 100-mm visual analogue scale (VAS) (mean difference (MD) 0.50, 95% confidence interval (CI) -0.84 to 1.84), improvement (risk ratio (RR) 0.96, 95% CI 0.54 to 1.70) or number of swollen joints on a scale from 0 to 28 (MD 0.60, 95% CI -0.90 to 2.10) (very low level of evidence). We found a very low level of evidence of reduction in the number of tender joints on a scale from 0 to 28 (MD -4.60, 95% CI -8.72 to -0.48; 16% absolute difference). We reported no physical disability and presented no data on withdrawals due to adverse events or on serious adverse events.

Two studies involving 194 participants with RA evaluated the effectiveness of additional radon in carbon dioxide baths. We found no statistically significant differences between groups for all outcomes at three-month follow-up (low to moderate level of evidence). We noted some benefit of additional radon at six months in terms of pain frequency (RR 0.6, 95% CI 0.4 to 0.9; 31% reduction; improvement in one or more points (categories) on a 4-point scale; moderate level of evidence) and 9.6% reduction in pain intensity on a 0 to 100-mm VAS (MD 9.6 mm, 95% CI 1.6 to 17.6; moderate level of evidence). We also observed some benefit in one study including 60 participants in terms of improvement in one or more categories based on a 4-point scale (RR 2.3, 95% CI 1.1 to 4.7; 30% absolute difference; low level of evidence). Study authors did not report physical disability, tender joints, swollen joints, withdrawals due to adverse events or serious adverse events.

One study involving 148 participants with RA compared balneotherapy (seated immersion) versus hydrotherapy (exercises in water), land exercises or relaxation therapy. We found no statistically significant differences in pain on the McGill Questionnaire or in physical disability (very low level of evidence) between balneotherapy and the other interventions. No data on improvement, tender joints, swollen joints, withdrawals due to adverse events or serious adverse events were presented.

One study involving 57 participants with RA evaluated the effectiveness of mineral baths (balneotherapy) versus Cyclosporin A. We found no statistically significant differences in pain intensity on a 0 to 100-mm VAS (MD 9.64, 95% CI -1.66 to 20.94; low level of evidence) at 8 weeks (absolute difference 10%). We found some benefit of balneotherapy in overall improvement on a 5-point scale at eight weeks of 54% (RR 2.35, 95% CI 1.44 to 3.83). We found no statistically significant differences (low level of evidence) in the number of swollen joints, but some benefit of Cyclosporin A in the number of tender joints (MD 8.9, 95% CI 3.8 to 14; very low level of evidence). Physical disability, withdrawals due to adverse events and serious adverse events were not reported.

Authors' conclusions

Overall evidence is insufficient to show that balneotherapy is more effective than no treatment, that one type of bath is more effective than another or that one type of bath is more effective than mudpacks, exercise or relaxation therapy.

PLAIN LANGUAGE SUMMARY

Balneotherapy (or spa therapy) for rheumatoid arthritis

We reviewed the evidence on the benefits and harms of balneotherapy (natural mineral waters, gases and mudpacks or spa therapy) in people with rheumatoid arthritis. Balneotherapy is defined as bathing in natural mineral or thermal waters (e.g. mineral baths, sulphur baths, Dead Sea baths), using mudpacks or doing both. Upon searching for all relevant studies up to December 2014, we found nine studies with 579 people. The quality of the evidence is very low mainly because of the low number of participants in the studies and concerns about study designs.

This review shows that in people with rheumatoid arthritis:

- we are uncertain whether mudpacks (balneotherapy) improve pain, overall wellness and swollen joints compared with placebo (fake treatment) in patients with hand RA. Mudpacks may improve tender joints slightly compared with placebo, but information about physical ability and adverse events was not reported in the study.
- adding radon to carbon dioxide baths did not improve pain intensity at three months but may improve overall well-being and pain at six months compared with carbon dioxide baths without radon, but this may have happened by chance. Information about physical disability, tender and swollen joints and adverse events was not reported in the studies.

Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

- we are uncertain whether balneotherapy (seated immersion) improves pain and physical function compared with hydrotherapy, exercise or relaxation. Improvement, tender joints, swollen joints and adverse events were not reported in the study.
- we are uncertain whether bathing in mineral baths (balneotherapy) improves pain and swollen joints compared with using a drug (Cyclosporin A). Mineral baths may improve overall wellness compared with Cyclosporin A, and Cyclosporin A may improve the number of tender joints compared with mineral baths. Physical disability and adverse events were not reported.
- we do not have precise information about side effects and complications of balneotherapy. This is particularly true for rare side effects. Side effects may include skin rash, infection and accidents, for example, slipping on wet surfaces near the bath area. The only study that reported side effects stated that they did not find any.

What is rheumatoid arthritis and what is balneotherapy?

When you have rheumatoid arthritis (RA), your immune system, which normally fights infection, inflames the lining of your joints, making them painful, stiff and swollen. The small joints of your hands and feet are usually affected first. No cure for RA is known at present, so treatments aim to relieve pain and stiffness while improving your ability to move.

Balneotherapy (bathing in water) is a type of therapy that aims to reduce pain and improve daily functioning. Balneotherapy often takes place at centres with thermal baths or seawater baths.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Balneotherapy compared with placebo for participants with rheumatoid arthritis

Balneotherapy compared with placebo for participants with rheumatoid arthritis

Patient or population: participants with rheumatoid arthritis

Settings: unclear

Intervention: balneotherapy (mineral-rich mud compresses)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Balneotherapy				
Pain intensity VAS, 0-100 (no pain to worst pain ever) Follow-up: 3 months	Mean pain intensity in control groups was 47	Mean pain intensity in intervention groups was 0.5 higher (0.84 lower to 1.84 higher)		45 (1 study)	⊕⊕⊕⊕ Very low a,b,c	MD 0.50 (95% CI -0.84 to 1.84) Absolute difference 0.5% (95% CI -0.84% to 1.84%) Relative percent change 1% (95% CI -2% to 4%) No statistically significant or clinically relevant difference
Improvement Yes/no based on 5 outcome measures (> 30% reduction in number of swollen joints, > 30% reduction in number of tender joints, > 20% improvement in patient VAS for severity of pain and > 20% improvement in physician VAS) Follow-up: 3 months	522 per 1000	501 per 1000 (282 to 887)	RR 0.96 (0.54 to 1.70)	45 (1 study)	⊕⊕⊕⊕ Very low a,b,c	Absolute difference -2% (95% CI -31% to 27%) Relative percent change 5% (95% CI -42% to 70%) No statistically significant or clinically relevant difference

Physical disability	See comment	See comment	Not estimable	-	See comment	Not reported
Not reported						
Tender joints	Mean number of tender joints in control groups was 12.5	Mean number of tender joints in intervention groups was 4.6 lower (8.7 lower to 0.5 higher)		45 (1 study)	⊕⊕⊕⊕ Very low ^{a,b,c}	MD -4.60 (95% CI -8.72 to -0.48) Absolute difference -16% (95% CI -31% to 2%) Relative percent change -37% (95% CI -70% to -4%) NNTB 32 (95% CI 10 to 717)
Number of painful joints						
Scale from 0 to 28						
Follow-up: 3 months						
Swollen joints	Mean number of swollen joints in control groups was 1.9	Mean number of tender joints in intervention groups was 0.6 higher (0.9 lower to 2.1 higher)		45 (1 study)	⊕⊕⊕⊕ Very low ^{a,b,c}	MD 0.60 (95% CI -0.90 to 2.10) Absolute difference 2% (95% CI -3% to 8%) Relative percent change 32% (95% CI -47% to 110%) No statistically significant or clinically relevant difference
Number of swollen joints						
Scale from 0 to 28						
Follow-up: 3 months						
Withdrawal due to serious adverse events	See comment	See comment	Not estimable	-	See comment	Not reported
Not reported						
Adverse events	See comment	See comment	Not estimable	-	See comment	Not reported
Not reported						

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NNTB**: Number needed to treat for an additional beneficial outcome; **RR**: Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded because of imprecision.

^bDowngraded because of a single study.

^cDowngraded because of design limitations.

Summary of findings 2. Additional radon in carbon dioxide baths compared with carbon dioxide baths only for participants with rheumatoid arthritis

Additional radon in carbon dioxide baths compared with carbon dioxide baths only for participants with rheumatoid arthritis

Patient or population: participants with rheumatoid arthritis

Settings: springs in Bad Brambach, Germany

Intervention: additional radon in carbon dioxide baths

Comparison: carbon dioxide baths only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Carbon dioxide baths only	Additional radon in carbon dioxide baths				
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 3 months	Mean change in pain intensity in control groups was -4.8 to 4.8	Mean change in pain intensity in intervention groups was 4.49 lower (13.41 lower to 4.44 higher)		194 (2 studies)	⊕⊕⊕⊖ Moderate ^a	MD -4.49 (95% CI -13.41 to 4.44) Absolute difference 4.5% (95% CI -13.4 to 4.4) No statistically significant or clinically relevant difference
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 6 months	Mean change in pain intensity in control groups was 0.7 to 7.9	Mean change in pain intensity in intervention groups was 9.59 lower (17.57 to 1.7 lower)		194 (2 studies)	⊕⊕⊕⊖ Moderate ^a	MD -9.59 (95% CI -17.57 to -1.6) Absolute difference 9.5% (95% CI -17.5 to -1.6) Statistically significant but not clinically relevant difference
Improvement More than 1 category change in pain intensity on 4-point scale (no pain/sporadic/daily/continuous) Follow-up: 3 months	267 per 1000	367 per 1000 (171 to 781)	RR 1.38 (0.64 to 2.93)	60 (1 study)	⊕⊕⊖⊖ Low ^{a,b}	Absolute difference 10% (95% CI -13% to 33%) Relative percent change 38% (95% CI -36% to 22%)

						No statistically significant or clinically relevant difference
Improvement More than 1 category change in pain intensity on 4-point scale (no pain/sporadic/daily/continuous) Follow-up: 6 months	233 per 1000	533 per 1000	RR 2.29 (1.1 to 4.74)	60 (1 study)	⊕⊕⊕⊖ Low ^{a,b}	Absolute difference 30% (95% CI 10% to 60%) Relative percent change 129% (95% CI 10% to 474%) Statistically significant and clinical relevant difference
Physical disability Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Tender joints Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Swollen joints Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Withdrawal due to serious adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Adverse events Not reported	See comment	See comment	Not estimable	-	See comment	Not reported

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded because of imprecision.

^bDowngraded because of a single study.

Summary of findings 3. Balneotherapy compared with drug treatment for participants with rheumatoid arthritis

Balneotherapy compared with drug treatment for participants with rheumatoid arthritis

Patient or population: participants with rheumatoid arthritis
Settings: Atatürk Rehabilitation and Balneotherapy Centre, Turkey
Intervention: balneotherapy
Comparison: drug treatment - Cyclosporin A

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Drug treatment - Cyclosporin A	Balneotherapy				
Pain intensity VAS, 0-100 mm (no pain to worst pain ever) Follow-up: 8 weeks	Mean pain intensity in control groups was 18	Mean pain intensity in intervention groups was 9.64 higher (1.66 lower to 20.94 higher)		57 (1 study)	⊕⊕⊕⊕ Very low a,b,c	MD 9.64 (95% CI -1.66 to 20.94) Absolute difference 10% (95% CI -2% to 21%) Relative percent change 53% (95% CI -9% to 116%) No statistically significant or clinically relevant difference
Improvement Global improvement on 5-point scale (very good/good/fair/poor/very poor) Follow-up: 8 weeks	400 per 1000	940 per 1000 (576 to 1000)	RR 2.35 (1.44 to 3.83)	57 (1 study)	⊕⊕⊕⊕ Very low a,b,c	Absolute difference 54% (95% CI 33% to 75%) Relative percent change 135% (95% CI 44% to 283%) NNTB 2 (95% CI 2 to 3)
Physical disability Not reported	See comment	See comment	Not estimable	-	See comment	Not reported
Tender joints Number of tender joints Scale from 0 to 28	Mean number of tender joints in control groups was 3.9	Mean number of tender joints in intervention groups was 8.9 higher (3.83 higher to 13.97 higher)		57 (1 study)	⊕⊕⊕⊕ Very low a,b,c	MD 8.90 (95% CI 3.83 to 13.97) Absolute difference 31% (95% CI 17% to 50%)

Follow-up: 8 weeks					Relative percent change 228% (95% CI 98% to 358%) NNTB 22 (95% CI 8 to 96)	
Swollen joints	Mean number of swollen joints in control groups was 1.9	Mean number of tender joints in intervention groups was 0.6 higher (1.25 lower to 4.25 higher)	57 (1 study)	⊕⊕⊕⊕ Very low ^{a,b,c}	MD 1.50 (95% CI -1.25 to 4.25)	
Number of swollen joints					Absolute difference 5% (95% CI -4% to 15%)	
Scale from 0 to 28					Relative percent change 79% (95% CI -66% to 224%)	
Follow-up: 8 weeks					No statistically significant or clinical relevant difference	
Withdrawal due to serious adverse events	See comment	See comment	Not estimable	-	See comment	Not reported
Not reported						
Adverse events	See comment	See comment	Not estimable	-	See comment	Not reported
Not reported						

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NNTB:** Number needed to treat for an additional beneficial outcome; **RR:** Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDowngraded because of single study.

^bDowngraded because of imprecision.

^cDowngraded because of design limitations.

BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation of the peripheral joints. In adults, the incidence of new cases is 50/100 000/y and one-year prevalence is between 500 and 600/100 000 (0.5% to 1.0%) (Symmons 1994). Common symptoms of RA consist of a combination of pain, fatigue, stiffness, reduced range of motion in the joints and muscle weakness. Inflammation can cause progressive destruction of articular and periarticular structures (McInnes 2011; Symmons 2002). RA can affect all joints in the body. The natural course of the disease is a slow but inexorable deterioration in physical condition, leading to difficulty in activities of daily living and poor quality of life. Rheumatoid arthritis is a multi-system disease that can affect internal organs, causing premature death. With adequate treatment targeted towards strongly reducing or abolishing inflammatory disease, many of these consequences can be prevented.

Description of the intervention

The term 'balneotherapy' comes from the Latin 'balneum' (bath). The term is classically used in (Eastern) European countries when natural mineral or thermal waters are used for bathing, drinking and inhalation. Recently a position paper was published with a proposal for, amongst others, a definition of balneotherapy (Gutenbrunner 2010). One of the core elements of balneotherapy is the use of (natural) mineral waters, gases and peloids (including packs = local application of peloids), often in health resorts (spas). In most European countries, balneotherapy often takes place at centres with thermal baths or seawater baths (Gutenbrunner 2010). In Israel, the main health resort area is located along the western shore of the Dead Sea. The unique environmental conditions in this area are considered beneficial for patients suffering from rheumatic disease (Sukenik 1994a).

In Homeric times, baths were applied primarily to cleanse and refresh. At the time of Hippocrates, bathing was regarded as more than a simple hygienic measure. It was considered beneficial in curing most illnesses (van Tubergen 2001). The Romans used water for treatment of orthopaedic conditions, but after the Roman era, spa therapy fell into disuse. In the sixteenth century, baths were rediscovered. Since that time, spa therapy has been practised continuously in the management of musculoskeletal conditions (Brosseau 2002; van Tubergen 2001; Verhagen 2007).

Balneotherapy is prescribed most often for patients with any form of arthritis, including fibromyalgia. Positive effects have been mentioned in the treatment of psoriasis as well (Brosseau 2002; Buskila 2001; Verhagen 2007).

Exercise in warm (tap) water is usually called 'hydrotherapy' or 'aquatic therapy'. This Cochrane review focuses on balneotherapy only, which consists of bathing in natural mineral or thermal waters, using mudpacks or doing both.

How the intervention might work

The mechanism by which balneotherapy might work is not clear. Water (thermal water, sea water) is generally used at a temperature of between 34°C and 36°C (Becker 2009; Gutenbrunner 2010). Hydrostatic force (Archimedes' principle) brings about relative pain

relief by reducing loading (Becker 2009); water reduces gravity in painful and rheumatic joints. The warmth and buoyancy of water may block nociception by acting on thermal receptors and mechanoreceptors (Bender 2005). Warm water may also enhance blood flow, which is thought to help in dissipating algogenic chemicals, and may facilitate muscle relaxation (Kamioka 2010). Apart from these mechanical and thermal mechanisms, one should not undervalue the psychological mechanisms of the spa environment. The related mental relaxation may also play a role in pain relief (Brosseau 2002).

The aim of balneotherapy is to improve the range of joint motion, relieve muscle spasm, maintain or improve functional mobility, soothe pain and, as a consequence, relieve patients' suffering and help them feel well (Fam 1991; Gutenbrunner 2010; Jagger 1984; Sukenik 1994a).

Why is it important to do this review?

No cure for RA is known at present, so treatment often focuses on management of symptoms such as pain, stiffness and mobility. Treatment options include pharmacological interventions (Colebatch 2011; Hurkmans 2009; Marks 2011; Richards 2012a; Richards 2012b; Ruiz Garcia 2011; Singh 2009; Singh 2010a; Singh 2010b; Whittle 2011), physical therapy (Brosseau 2003; Han 2004) and balneotherapy (Verhagen 2008). Since our last publication of this Cochrane review (Verhagen 2008), several systematic reviews and meta-analyses on the effectiveness of balneotherapy have been published (Falagas 2009; Forestier 2008; Kamioka 2010). These reviews either combine balneotherapy and hydrotherapy (Forestier 2008; Kamioka 2010) or combine different diseases (Falagas 2009).

Despite its popularity, reported scientific evidence on the effectiveness or efficacy of balneotherapy is sparse. This review evaluates the benefits and harms of balneotherapy in patients with RA.

OBJECTIVES

To perform a systematic review on the benefits and harms of balneotherapy in patients with rheumatoid arthritis in terms of pain, improvement, disability, tender joints, swollen joints and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were eligible if they were randomised controlled trials (RCTs).

Types of participants

Participants had rheumatoid arthritis (RA), with definitive or classical RA as defined by the American Rheumatism Association (ARA) criteria of 1958 (Ropes 1958), the ARA/American College of Rheumatology (ACR) criteria of 1988 (Arnett 1988) or the ACR/European League Against Rheumatism (EULAR) criteria of 2010 (Aletaha 2010), or by studies using the criteria of Steinbrocker (Steinbrocker 1949).

Types of interventions

Balneotherapy had to be the intervention under study, and had to be compared with another intervention or with no intervention. Balneotherapy is defined as bathing in natural mineral or thermal waters (e.g. mineral baths, sulphur baths, Dead Sea baths), using mudpacks or doing both.

Types of outcome measures

Major outcomes

The World Health Organization (WHO) and the International League Against Rheumatism (ILAR) determined in 1992 a core set of eight endpoints for clinical trials concerning patients with RA (Boers 1994). Major outcomes that we will consider are pain, improvement, disability, tender joints, swollen joints, withdrawals due to adverse events and serious adverse events.

Minor outcomes

Other outcomes that we considered include patient global assessment, physician global assessment, stiffness, range of motion, activities of daily living, quality of life, morning stiffness, walk time, hand grip strength and Ritchie index.

We considered all major outcomes and presented results in the 'Summary of findings' tables.

Search methods for identification of studies

Electronic searches

We searched the Cochrane 'Rehabilitation and Related Therapies' Field Register (to December 2014), the Cochrane Central Register of Controlled Trials (2013, Issue 1), MEDLINE (1950 to December 2014), EMBASE (1988 to December 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to December 2014), the Allied and Complementary Medicine Database (AMED) (1985 to December 2014), PsycINFO (1806 to December 2014) and the Physiotherapy Evidence Database (PEDro) (to December 2014). We applied no language restrictions, but studies not reported in English, Dutch, Danish, Swedish, Norwegian, German or French are awaiting assessment.

We also searched the [WHO International Clinical Trials Registry Platform](#) for ongoing and recently completed trials.

In MEDLINE, the subject-specific strategy was combined with the sensitivity- and precision-maximising version of the Cochrane Highly Sensitive Search Strategy (Higgins 2011a) used to identify randomised trials in MEDLINE and modified for use in other databases.

Search strategies performed in MEDLINE, CENTRAL, EMBASE and CINAHL are presented in [Appendix 1](#).

Searching other resources

We also searched the reference lists of articles and contacted experts in the field.

Data collection and analysis

Selection of studies

Initially, two review authors (SMAB-Z, JL) independently selected trials by inspecting titles, keywords and abstracts to determine

whether studies met the inclusion criteria regarding design, participants and interventions. We retrieved for final assessment full publications of studies of any possible relevance. Next, we used a standardised form to independently perform the final selection of trials to be included in the review. We resolved disagreements by consensus and, if necessary, by third party adjudication (APV).

Data extraction and management

Two review authors (JRC, JL) independently extracted data on trial methods, participants, interventions, types of outcome measures, duration of follow-up, loss to follow-up and results using a standardised data extraction form. We resolved disagreements by consensus and, if necessary, by third party adjudication (APV). We contacted trial authors when further information was required to complete the data extraction form.

Assessment of risk of bias in included studies

Two review authors (RAdB, HCWdV) independently assessed risk of bias by using the assessment tool developed by The Cochrane Collaboration (Higgins 2011a). This tool involves assessment of randomisation (sequence generation and allocation concealment), blinding (of participants, care providers and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias (baseline comparability, co-interventions, compliance, timing of outcome measures). All items could be scored as having high, low or unclear risk of bias. We resolved disagreements by consensus; if disagreement persisted, a third review author (APV) made a final decision. We contacted trial authors if further information was required.

Measures of treatment effect

We presented various outcome measures separately. For dichotomous data, we expressed results, if possible, as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). We calculated mean differences (MDs) or, when scales for outcome measures were dissimilar, standardised mean differences (SMDs) with 95% confidence intervals for continuous data (Lau 1997).

Unit of analysis issues

Treatment allocation was done at an individual level in all trials, and no cluster-randomised or cross-over trials were found, so the unit of analysis was the individual participant.

Dealing with missing data

When possible, we contacted trial authors to request missing data, and we performed intention-to-treat analyses to include all randomly assigned participants. For dichotomous data, we performed a worst-case scenario when all missing people in the intervention group had a bad outcome, although none of the missing people in the control group had such an outcome. However for continuous data, when dropouts were identified, we used the actual number of participants contributing data at the relevant outcome assessment. Unless missing standard deviations could be derived from confidence intervals or standard errors (from the same study), we did not assume values for the purpose of presenting them in the analyses.

Assessment of heterogeneity

We assessed heterogeneity between pooled trials by using a combination of visual inspection of graphs and consideration of the

I^2 statistic ([Higgins 2003](#)). Substantial heterogeneity is defined as I^2 greater than 50%.

Assessment of reporting biases

Available data are insufficient for assessment of publication bias via a prepared funnel plot, so publication bias cannot be assessed.

Data synthesis

We used RevMan Analyses (RevMan5) to analyse the data. In the previous review ([Verhagen 2008](#)), review authors did not pool data because the included trials were considered clinically heterogeneous in terms of study populations and interventions. Should pooling be possible with new trials included, we will pool results of comparable groups of trials by using a random-effects model and 95% confidence intervals.

Subgroup analysis and investigation of heterogeneity

Preplanned stratified analyses included:

- trials comparing balneotherapy versus no treatment or waiting list controls;
- trials comparing different types of balneotherapy; and
- trials comparing balneotherapy versus other treatment(s) (e.g. exercise, oral medication).

Sensitivity analysis

A preplanned sensitivity analysis involved the risk of bias items of concealed randomisation and blinding.

'Summary of findings' table

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of evidence ([Higgins 2011b](#)). The quality of the evidence was based upon five domains and was downgraded by one level for each of these factors when encountered: (1) limitations in design,

(2) indirectness of evidence (i.e. generalisability of findings), (3) unexplained heterogeneity or inconsistency of results (significant statistical heterogeneity ($I^2 > 50\%$) or inconsistent findings among studies), (4) imprecision (total number of participants < 300 for each outcome) and (5) high probability of publication bias. Two review authors (SMSB-Z,APV) determined these factors. We considered single randomised studies ($n < 300$ for dichotomous outcomes and $n < 400$ for continuous outcomes) to be inconsistent and imprecise and to provide "low-quality evidence", which could be further downgraded to "very low-quality evidence" for limitations in design (i.e. high risk of bias), indirectness or other considerations. We applied the following levels of quality of evidence.

- High quality: Further research is very unlikely to change the level of evidence. Data are sufficient and have narrow confidence intervals. No reporting biases are known or suspected; all domains were fulfilled.
- Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; one of the domains was not fulfilled.
- Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; two of the domains were not fulfilled.
- Very low quality: Great uncertainty surrounds the estimate; three of the domains were not fulfilled.

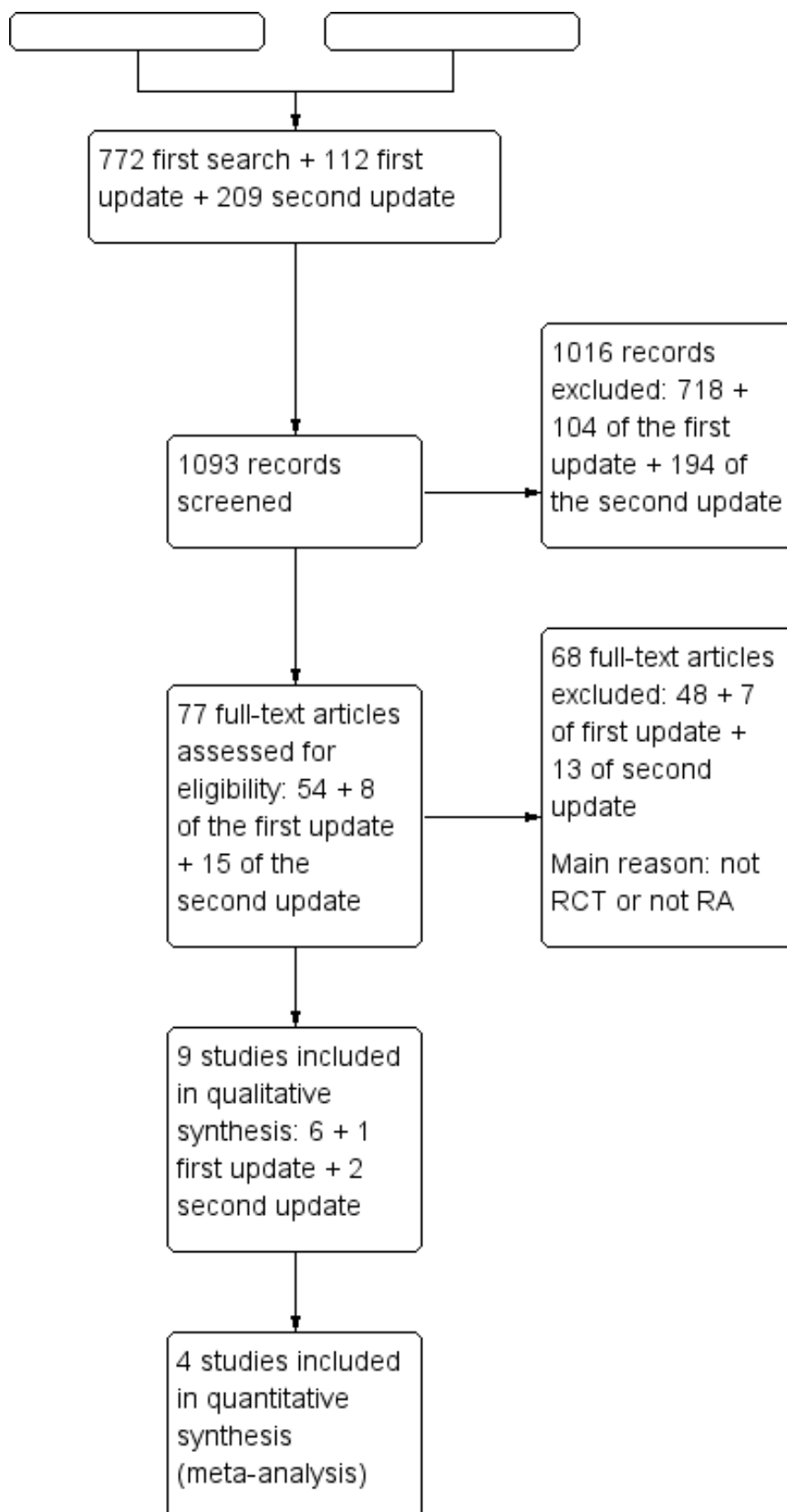
RESULTS

Description of studies

Results of the search

A search conducted for this update resulted in 210 references, from which two review authors (JL, APV) independently selected 16 additional references on the basis of title and abstract. Of these, two studies were found to be eligible on the basis of full paper assessment and were included in this review ([Codish 2005](#); [Franke 2007](#)); see study flow chart in [Figure 1](#).

Figure 1. Study flow diagram.



Included studies

Final selection based on consensus resulted in inclusion of nine studies in this review, of which five were of Israeli origin, although they were written in English (Codish 2005; Elkayam 1991; Sukenik 1990a; Sukenik 1990b; Sukenik 1995).

Participants

A total of 579 participants were enrolled, and the number of participants in the intervention groups ranged from eight to 67 (see [Characteristics of included studies](#)). In six of the nine studies, the smallest study arm included fewer than 30 participants, meaning that most studies were underpowered. In seven studies, researchers used ARA criteria when selecting participants, and in two studies, they used the Steinbrocker criteria (Hall 1996; Yurtkuran 1999). All studies included participants with RA as defined by ARA or Steinbrocker criteria, although the severity of RA differed slightly between studies. When mentioned, the percentage of males was between 5% and 40%, and mean age ranged from 39 to 62.4 years.

Interventions

Six studies had two treatment arms, and the other three studies had four treatment arms. Only once was a placebo control used in comparison with mudpacks (Codish 2005). In two studies, a no-treatment control group was used (Sukenik 1990b; Sukenik 1995). In both studies, participants were aware of the fact that they did not receive baths as treatment. In one other study, the drug treatment group was the control group (Yurtkuran 1999). In all but one study (Hall 1996), the intervention included mineral baths, and in one study, the intervention was given in combination with mudpacks (Elkayam 1991). Two studies evaluated Dead Sea baths (Sukenik 1990a; Sukenik 1995), and two studies evaluated the added value of radon over carbon dioxide in the bath (Franke 2000; Franke 2007).

In all studies, the baths were prepared at between 35°C and 38°C. All participants continued their medication during balneotherapy. One study mentioned standardised exercise therapy (Hall 1996), and in another study, relaxation exercises were allowed (Yurtkuran 1999).

All studies but one were performed at spa resorts; only Codish (Codish 2005) provided mudpacks (and placebo mudpacks) to be used at home.

Outcome measures

All studies used several outcome measures including pain and function. Often a standard set of outcome measures was used, such as duration of morning stiffness, 15-meter walk time, hand grip strength, Ritchie index, severity of disease as assessed by participant or physician and laboratory variables. In two studies (Franke 2000; Hall 1996), investigators used a 'quality of life' instrument (Arthritis Impact Measurement Scales (AIMS) or AIMS2). Three studies (Codish 2005; Franke 2000; Yurtkuran 1999) reported response to treatment or improvement, but investigators in different studies defined it differently (see [Characteristics of included studies](#)).

The overall follow-up period was three months; only two studies reported six-month follow-up (Franke 2000; Franke 2007).

Excluded studies

From the total search, 21 studies are awaiting assessment because of their language of publication (19 first review, two first update); 21 studies were excluded because they appeared not to be RCTs (16 first review, two first update and three second update); 18 were excluded because they did not concern RA (12 first review, two first update and four second update) and eight because of the outcome measures selected (one first review, one first update and six second update).

Risk of bias in included studies

Four studies described their randomisation procedure; three of these studies were considered to use a concealed randomisation procedure (Franke 2000; Franke 2007; Hall 1996) (Figure 2 and Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

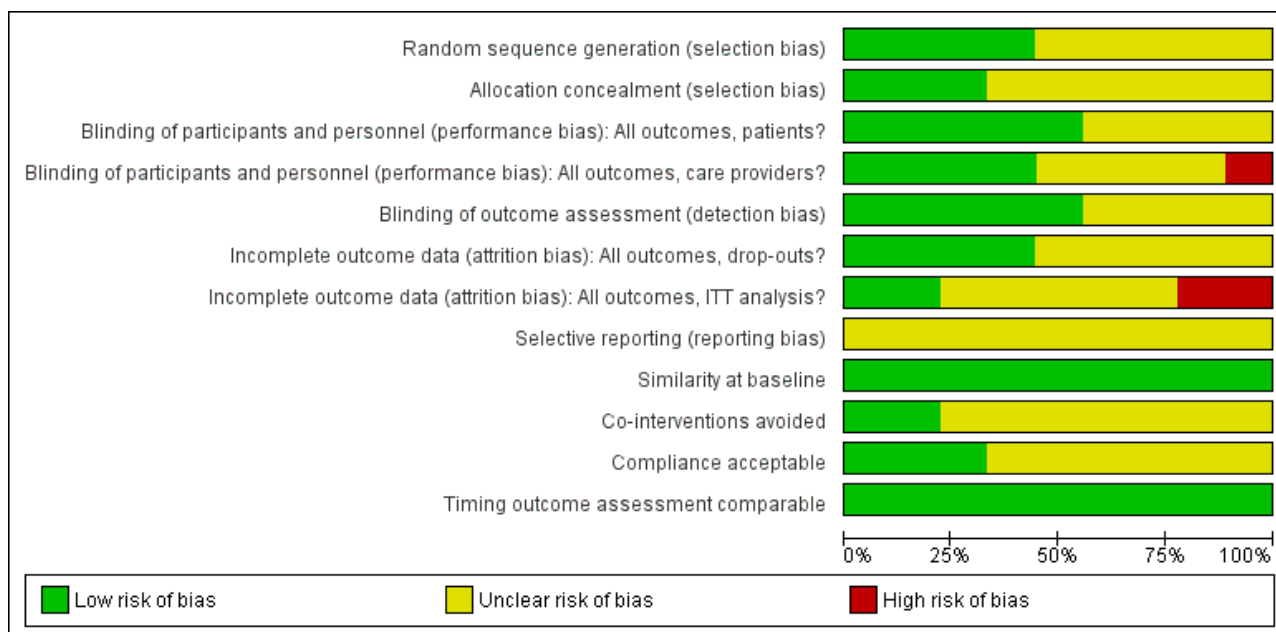


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes, patients?	Blinding of participants and personnel (performance bias): All outcomes, care providers?	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias): All outcomes, drop-outs?	Incomplete outcome data (attrition bias): All outcomes, ITT analysis?	Selective reporting (reporting bias)	Similarity at baseline	Co-interventions avoided	Compliance acceptable	Timing outcome assessment comparable
Codish 2005	?	?	+	+	+	+	?	?	+	?	?	+
Elkayam 1991	?	?	+	?	+	+	+	?	+	?	?	+
Franke 2000	+	+	+	+	+	?	-	?	+	+	+	+
Franke 2007	+	+	+	+	+	+	+	?	+	+	+	+
Hall 1996	+	+	?	-	?	+	-	?	+	?	?	+
Sukenik 1990a	+	?	+	+	+	?	?	?	+	?	+	+
Sukenik 1990b	?	?	?	?	?	?	?	?	+	?	?	+
Sukenik 1995	?	?	?	?	?	?	?	?	+	?	?	+
Yurtkuran 1999	?	?	?	?	?	?	?	?	+	?	?	+

Blinding of the observer/outcome assessor is mentioned in all studies, but in several studies, the participant reported the main outcome, and it was unclear whether the participant was blinded, which means that we scored blinding of the outcome assessor as unclear (unclear risk of bias) (Hall 1996; Sukenik 1990b; Sukenik 1995; Yurtkuran 1999). Four studies mentioned blinding of the caregiver (Codish 2005; Franke 2000; Franke 2007; Sukenik 1990a), but the success of blinding was never evaluated.

Two studies were scored as having low risk of bias on 'other biases' because study authors clearly mentioned that groups were comparable at baseline, co-interventions were comparable and compliance was acceptable (Franke 2000; Franke 2007).

Only three studies were considered to have no limitations in design, meaning a low risk of bias in most domains (Franke 2000; Franke 2007; Sukenik 1990a). In terms of the risk of bias assessment, the kappa between two review authors appeared to be moderate at 0.68.

Effects of interventions

See: [Summary of findings for the main comparison Balneotherapy compared with placebo for participants with rheumatoid arthritis](#); [Summary of findings 2 Additional radon in carbon dioxide baths compared with carbon dioxide baths only for participants with rheumatoid arthritis](#); [Summary of findings 3 Balneotherapy compared with drug treatment for participants with rheumatoid arthritis](#)

Data presented in the papers, even after communication with the study authors, were too scarce to enable 'between-group' analysis in almost half the studies. Also the studies used different interventions or comparison treatments and a wide variety of outcome measures; therefore interventions and outcome measures were considered heterogeneous.

One study assessed arms of balneotherapy (Yurtkuran 1999); only one participant complained of headache. In this study, most side effects were found in the control group (Cyclosporin A); between 4% and 16% of participants experienced various side effects such as gastrointestinal disturbance (one participant; 4%) and nephrotoxicity (four participants; 16%) (Yurtkuran 1999).

Trials comparing balneotherapy versus placebo or no treatment/waiting list controls

One study (n = 45) compared mudpacks versus placebo mudpacks for hand RA (Codish 2005).

We found no statistically significant differences between groups in terms of pain intensity (MD 0.50, 95% CI -0.84 to 1.84; absolute difference 0.5%), improvement (or 'response rate') (RR 0.96, 95% CI 0.54 to 1.70; absolute difference -2%) and number of tender joints (MD -4.60, 95% CI -8.72 to -0.48; absolute difference -16%) (Analysis 1.1; Analysis 1.2; Analysis 1.3; Summary of findings for the main comparison). Therefore we conclude that very low-level evidence (single study, downgraded by design) showed unclear benefit of mudpacks over placebo in hand RA in terms of pain, response rate and number of tender joints. Physical disability was not reported. Also no data were presented on improvement, withdrawals due to adverse events or serious adverse events.

Two studies (n = 76) included a control group receiving no treatment (Sukenik 1990b; Sukenik 1995). Both studies suffer from high risk of bias and low power; short-term improvement was mentioned in all treatment groups compared with control groups for most outcome measures (see [Characteristics of included studies](#)). No data were provided on pain, improvement, physical disability, number of tender and swollen joints, withdrawals due to adverse events or serious adverse events. The study authors' conclusion of improvement was based on pre/post analysis. Data on harm or side effects were not reported.

Trials comparing different types of balneotherapy

Three studies compared mineral baths versus tapwater baths (Elkayam 1991; Franke 2000; Franke 2007). We were able to pool the data from two studies (n = 194) evaluating the effectiveness of additional radon in carbon dioxide baths (Franke 2000; Franke 2007).

We found no statistically significant differences post treatment and at three months in pain intensity on a VAS, but a statistically significant difference in pain in favour of additional radon at six-month follow-up only, with a difference of 9.6 mm on a 100-mm VAS (95% CI 1.6 to 17.6). Both effect estimates show no clinically relevant differences (> 15%) (Analysis 2.1; Summary of findings 2).

We found no differences post treatment and at three months in terms of improvement in pain frequency on a 4-point scale (no, sporadic, daily, continuous) or improvement in one or more categories, but a significant difference of only 30% in favour of additional radon at six-month follow-up (RR 2.3, 95% CI 1.1 to 4.7) (Analysis 2.2; Summary of findings 2).

For all other outcomes (physical disability, tender joints, swollen joints, withdrawals due to adverse events and serious adverse events), no data were provided.

Therefore we conclude that moderate-level evidence (downgraded because of imprecision (low power)) shows unclear benefit in terms of pain at end of treatment and at three-month follow-up, but benefit of additional radon in carbon dioxide baths for the treatment of participants with RA at six months, although the clinical relevance of this benefit is small. We found low-level evidence (single study) of unclear benefit for improvement at end of treatment and at three-month follow-up, but benefit of additional radon in carbon dioxide baths in the treatment of patients with RA at six months.

Two studies (n = 76) compared Dead Sea salt baths versus normal salt baths (Sukenik 1990a) or sulphur baths (Sukenik 1995), and another study (n = 30) compared sulphur baths versus mudpacks (Sukenik 1990b). All three studies did not provide sufficient data on pain, improvement, physical disability, number of tender and swollen joints, withdrawal due to adverse events and serious adverse events for the analysis. The authors of original studies mentioned short-term improvement in all treatment groups on most outcome measurements, but a more profound effect in the groups receiving mineral baths. All studies were of low power, performed a pre/post analysis and presented only point estimates.

Trials comparing balneotherapy versus other treatments (e.g. exercise, oral medication)

In one study ($n = 35$ in each study arm), 'balneotherapy' (seated immersion) was compared with hydrotherapy (exercise in water), land exercise or relaxation therapy (Hall 1996). Here balneotherapy was performed with tapwater at 36°C (Analysis 3.1).

We found no statistically significant differences in pain (MD 0.05, 95% CI -0.32 to 0.42) and physical disability (MD -0.70, 95% CI -1.50 to 0.10). No data were provided on improvement, tender joints, swollen joints, withdrawal due to adverse events or serious adverse events.

Therefore we conclude that a very low level of evidence (single study and downgraded because of limitations in design (high risk of bias)) shows unclear benefit of tapwater bathing over relaxation, exercise or hydrotherapy.

In another study ($n = 57$), balneotherapy was compared with drug therapy (Cyclosporin A (CsA) 3.5 mg/kg) (Yurtkuran 1999). We found no statistically significant differences in terms of pain (0 to 100 VAS) (MD 8, 95% CI -17.54 to 1.54) or swollen joints (MD 1.50, 95% CI -1.25 to 4.25) (Analysis 3.2; Summary of findings 3). We found a statistically significant benefit of mineral baths in terms of overall improvement at eight weeks of 54% (RR 2.35, 95% CI 1.44 to 3.83) (Analysis 3.3) and significant benefit of Cyclosporin A at eight weeks in terms of the number of tender joints (MD 8.9, 95% CI 3.8 to 14) (Analysis 3.4; Summary of findings 3). For all other outcome measures (physical disability, withdrawal due to adverse events and serious adverse events), no data were provided.

Very low-level evidence (single study and downgraded because of limitations in design (high risk of bias)) suggests some benefit of mineral baths over Cyclosporin A concerning overall improvement, and of Cyclosporin A over mineral baths in terms of the number of swollen joints.

DISCUSSION

Summary of main results

This review evaluated the benefits and harms of balneotherapy in patients with RA. Concerning pain, number of tender joints, 'response rate' or improvement, no statistically significant differences were found between mudpacks for the hand and placebo mudpacks (very low level of evidence) or for bathing with tapwater over relaxation, exercise or hydrotherapy (very low level of evidence). Harms were not reported for this comparison.

In terms of pain, some benefit has been associated with additional radon in carbon dioxide baths for the treatment of patients with RA, but the clinical relevance of this benefit is small (moderate level of evidence). Regarding all other outcome measures (improvement, disability, tender joints, swollen joints, withdrawal due to adverse events or serious adverse events), we conclude that the benefit of either form of balneotherapy over another is inconclusive.

For pain, a very low level of evidence of unclear benefit was found. For overall improvement, we found some benefit of balneotherapy over drug treatment (very low level of evidence). In this comparison, withdrawals due to adverse events were not reported.

Overall completeness and applicability of evidence

Rheumatoid arthritis (RA) is a chronic, progressive and disabling disease that has great impact on quality of life. When balneotherapy is evaluated, the outcome measures used and the follow-up period chosen should be adequate. The main aims of balneotherapy are to maintain or improve functional mobility, soothe pain and let patients feel well. Often a standard set of outcome measures was used. In daily life, patients are trying to deal with pain by using coping strategies. Pain (often assessed by the patient) was reported as an outcome measure in the Methods sections of most studies, but results were seldom reported. A 'quality of life' assessment was reported in only two studies (Franke 2000; Hall 1996). This is surprising because one of the aims of balneotherapy, or therapy for patients with chronic disease in general, is to improve health-related 'quality of life'. The question can be raised whether the outcome measures used in most studies were specific and responsive enough to enable measurement of treatment effect. Also the follow-up period seems to be rather short. Positive effects of spa therapy have been found in patients with ankylosing spondylitis even after 40 weeks of follow-up (van Tubergen 2001).

We noted heterogeneity of the intervention 'balneotherapy'. Once balneotherapy consisted of tapwater, once as mineral baths (38°C, daily for 20 minutes) + mudpacks (for 20 minutes), twice as radon/carbon dioxide baths (15 times in four weeks, for 20 minutes), twice as Dead Sea baths (daily for 20 to 30 minutes), twice as sulphur baths (daily for 20 minutes), once as a combination of Dead Sea and sulphur baths, once as a combination of sulphur baths + mudpacks (see table of included studies) and once as only mudpacks. This makes it difficult to determine what the most effective form of balneotherapy is, or even whether an essential element (minerals) in the water is responsible for its effectiveness.

Quality of the evidence

Unfortunately, most studies showed methodological flaws resulting in high risk of bias. Also data presentation was often lacking. When information concerning trial design, especially regarding strategies to avoid bias, is lacking, we could not exclude possible bias in the trial. Therefore, a robust analysis of the effectiveness of balneotherapy cannot be presented.

Potential biases in the review process

Our review might very well suffer from selection bias based on language. We found several studies that were presented in Hebrew, Japanese or one of the Eastern European languages. Often the English abstract was lacking information about the design of the study. These studies are all awaiting assessment.

We used the criteria of the Cochrane Back Review Group (CBRG) for risk of bias assessment (Furlan 2009). This tool is a slightly extended version of the one described in the *Cochrane Handbook for Systematic Reviews of Interventions*, although with some sub-items in the different domains, easing the risk of bias assessment. In previous versions of the review, we used the Delphi list, which is comparable with the risk of bias assessment tool of the CBRG (Verhagen 1998). Therefore we observed no major differences concerning risk of bias assessment between the previous version and the current version of the review. Overall this risk of bias assessment tool can be regarded as a reliable and valid instrument (Furlan 2009; Verhagen 2001). Nevertheless misclassification is always a possibility.

The 'spa environment' is an important factor in treatment results (Balint 1993; Sukenik 1994a). Many factors may contribute positively to reported effects (Fam 1991), such as changes in environment, the 'spa scenery', absence of (house)work duties, physical and mental relaxation, the non-competitive atmosphere with similarly suffering companions, physical therapy and so forth. As such, any benefit of the spa could perhaps be attributed also to the effects of factors unrelated to the "water" therapy per se.

Agreements and disagreements with other studies or reviews

The conclusion of this review that evidence is still insufficient to show the effectiveness of balneotherapy is consistent with the conclusion of other reviews (Brosseau 2002; Kamioka 2010; Karagülle 2004). Although the selection criteria differ between reviews, all review authors conclude that poor methodological quality and scarce data presentation make it impossible to draw firm conclusions. The more recent studies are of better methodological rigour, but additional studies are needed.

AUTHORS' CONCLUSIONS

Implications for practice

Balneotherapy is one of the oldest forms of therapy for patients with arthritis. On pain, we found a low level of evidence of benefit for mineral baths when compared with drug treatment at eight weeks and a moderate level of evidence of benefit of additional radon in carbon dioxide baths for the treatment of patients with RA. Most studies report positive findings but provide insufficient evidence to support their claims. Scientific evidence is insufficient because of high risk of bias in most studies and absence of an adequate statistical analysis.

Implications for research

- Large studies with low risk of bias are needed, focusing on appropriate allocation concealment, blinding and adequate data presentation and analysis. The design and reporting of future trials should conform to CONSORT guidelines.
- New research should at a minimum use the agreed upon core set of outcome measures for RA supplemented with further specific measures relevant to capture the patient experience, documented to be adequate with the patient responsive to the treatment under study. Follow-up should be of sufficient length to assess long-term effects.
- New research should provide full data on outcome measures, including mean and standard deviation or 95% confidence interval.
- Future research should examine the effects of balneotherapy not only in pragmatic trials comparing various interventions with each other, but also in more explanatory trials comparing intervention groups versus a no-treatment control group. When possible, the beneficial effect of the 'spa environment' should be considered as a confounder or an effect modifier and accounted for in the design of the trial.

We conclude that performing randomised studies with low risk of bias concerning the effectiveness of balneotherapy is both possible and necessary to provide strong evidence on the effects of balneotherapy.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Codish 2005

Methods	RCT, double-blind
Participants	Patients with RA, according to ARA criteria, and with active arthritis of the wrist, metacarpophalangeal joints and/or proximal interphalangeal joints Israel; n = 45
Interventions	Group I: mineral-rich mud compresses; n = 23 Group II: mineral-depleted mud compresses; n = 23 Groups were matched for age, etc Treatment for 3 weeks; 15 treatments of 20 minutes
Outcomes	The number of swollen and tender joints of both hands; participant assessment of overall joint pain severity on a visual analogue scale; physician global assessment of disease activity on a visual analogue scale Response to therapy (improvement) is a combination of all outcome measures into yes/no response to treatment Outcome assessment at 3 weeks (after treatment), 1 month and 3 months after treatment
Notes	This study was supported in part by a grant from the Ahava Company, Dead Sea Laboratories, Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes, patients?	Low risk	Neither participants nor physicians were aware of which type of compresses were used
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Low risk	Neither participants nor physicians were aware of which type of compresses were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome was assessed by the participant, who was blinded
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Low risk	No mention of dropouts; seems to be an available case analysis
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Unclear risk	ANOVA repeated measurements (intention-to-treat)

Codish 2005 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Unclear compliance rate
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

Elkayam 1991

Methods	RCT Blinding: participant
Participants	Physician/rheumatologist Israel; n = 41 RA as defined by ARA
Interventions	I: mineral baths + mudpacks, n = 19; 5% male; mean age 57.7 years; mean DOC 13 years C: tapwater baths, n = 22; 14% male; mean age 60.3 years; mean DOC 12.9 years Treatment duration: 2 weeks; follow-up: 12 weeks
Outcomes	Morning stiffness (minutes), 15-meter walking time (seconds), hand grip strength (mm Hg), ADL (6-point scale), number of active joints, Richie index, participant assessment (7-point scale), physician assessment (7-point scale)
Notes	Only point estimates, no measures of variability presented No information on funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear randomisation method
Allocation concealment (selection bias)	Unclear risk	No description of concealment
Blinding of participants and personnel (performance bias) All outcomes, patients?	Low risk	Participants were blinded: the 2 groups were treated separately and were not aware that they received different modalities
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Unclear risk	Blinding of care providers is unclear

Elkayam 1991 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were blinded; therefore outcome assessment is blinded
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Low risk	No mention of dropouts; seems to be an available case analysis
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Low risk	ANOVA repeated measurements (intention-to-treat)
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Unclear compliance rate
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

Franke 2000

Methods	RCT Blinding: participant, caregiver and observer
Participants	In-patient rehabilitation centre Bad Brambeck, Germany; n = 60 RA as defined by ARA
Interventions	I: radon + carbon dioxide baths, n = 30; 27% male; mean age 58 years; mean DOC 11 years C: carbon dioxide baths only, n = 30; 20% male; mean age 58 years; mean DOC 9.9 years Treatment duration: 4 weeks; follow-up: 3 months and 6 months
Outcomes	Pain (VAS), global status (AIMS), function (Keitel function index), morning stiffness (minutes), improvement in more than 1 pain category and in laboratory variables
Notes	1 dropout, 3 incomplete follow-up; no side effects No information on funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table randomisation list
Allocation concealment (selection bias)	Low risk	Randomisation done by independent researcher; participants received barcode

Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

Franke 2000 (Continued)

Blinding of participants and personnel (performance bias) All outcomes, patients?	Low risk	Participants were unaware of treatment allocation
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Low risk	Therapists were unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were blinded, so outcome assessment was blinded Investigators were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Unclear risk	Low dropout rate (7%)
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	High risk	No intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Low risk	Co-interventions were comparable
Compliance acceptable	Low risk	Compliance was acceptable
Timing outcome assessment comparable	Low risk	Timing was comparable

Franke 2007

Methods	RCT Blinding: participant, caregiver and observer
Participants	In-patient rehabilitation centre Bad Brambeck, Germany; n = 134 RA as defined by ARA
Interventions	I: radon + carbon dioxide baths, n = 67; 32% male; mean age 58.3 years; mean DOC 12 years C: carbon dioxide baths only, n = 67; 30% male; mean age 54.1 years; mean DOC 10 years Treatment duration: 3 weeks; follow-up: 3 months and 6 months
Outcomes	Pain (VAS), pain frequency, function (Hanover functional capacity test, Keitel function index), morning stiffness (minutes), pain medication
Notes	Dropouts in intervention group: n = 3; in control group: n = 7

Franke 2007 (Continued)

No information on funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table randomisation list
Allocation concealment (selection bias)	Low risk	Randomisation done by independent researcher; participants received barcode
Blinding of participants and personnel (performance bias) All outcomes, patients?	Low risk	Participants were unaware of treatment allocation
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Low risk	Therapists were unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants were blinded, so outcome assessment was blinded Investigators were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Low risk	Low dropout rate (7%)
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Low risk	Intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Low risk	Co-interventions were comparable
Compliance acceptable	Low risk	Compliance was acceptable
Timing outcome assessment comparable	Low risk	Timing was comparable

Hall 1996

Methods	RCT Blinding: observer, not the participant
Participants	Outpatient clinic hospital Bath, UK; n = 148

Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

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Hall 1996 (Continued)

Chronic RA; Steinbrocker class I, II and III

Interventions	I: seated immersion, n = 35; 40% male; mean age 55.8 years, mean DOC 9.7 years C1: hydrotherapy, n = 35; 23% male; mean age 58.5 years; mean DOC 11.9 years C2: land exercise, n = 34; 31% male; mean age 58.7 years; mean DOC 12.2 years C3: relaxation, n = 35; 28% male; mean age 59.8 years; mean DOC 12.2 years Treatment duration: 4 weeks; follow-up: 3 months
Outcomes	Pain (McGill), ROM, grip strength, joint tenderness, morning stiffness, global status (AIMS2), participant and therapist self assessment
Notes	9 dropouts; pre/post analysis Funded by the Arthritis and Rheumatism Council and the Chartered Society of Physiotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using random number table
Allocation concealment (selection bias)	Low risk	Randomisation by independent co-ordinator
Blinding of participants and personnel (performance bias) All outcomes, patients?	Unclear risk	Unclear whether participant was blinded, probably not
Blinding of participants and personnel (performance bias) All outcomes, care providers?	High risk	Therapists were not blinded; 3 therapists performed interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessor was blinded, but unclear whether participant was blinded
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Low risk	139 out of 148 completed the study and were included in analyses (6% dropouts)
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	High risk	No intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Unclear compliance rate

Hall 1996 (Continued)

Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable
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Sukenik 1990a

Methods	RCT Blinding: participant and observer
Participants	Outpatient clinic Soroka, Israel; n = 30 RA as defined by ARA
Interventions	I: Dead Sea salt baths, n = 15; 13% male; mean age 57 years; mean DOC 13.4 years C: sodium chloride baths, n = 15; 26% male; mean age 58.4 years; mean DOC 11 years Treatment duration: 2 weeks; follow-up: 3 months
Outcomes	Larger improvement, mostly in I compared with C, in morning stiffness, 15-meter walking time, hand grip strength, Ritchie index, number of active joints, activities of daily living, participant self assessment
Notes	Pre/post analysis, only point estimated presented 4 cases of mild side effects in I (thermal reaction) No information on funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of random number table
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes, patients?	Low risk	Neither the participant nor the rheumatologist knew the nature of the baths
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Low risk	Neither the participant nor the rheumatologist knew the nature of the baths
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither the participant nor the rheumatologist knew the nature of the baths, so outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Unclear risk	No mention of dropouts; seems to be an available case analysis

Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

Sukenik 1990a (Continued)

Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Unclear risk	Unclear whether intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Low risk	Compliance was satisfactory
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

Sukenik 1990b

Methods	RCT Blinding: observer
Participants	Outpatient clinic Soroka, Israel; n = 40 RA as defined by ARA
Interventions	I: sulphur baths, n = 10; 10% male; mean age 56.8 years; mean DOC 10.3 years C1: mudpacks, n = 10; 30% male; mean age 49 years; mean DOC 6.4 years C2: mudpacks + sulphur baths, n = 10; 10% male; mean age 52.3 years; mean DOC 8.2 years C3: no-treatment control, n = 10; 30% male; mean age 52.4 years; mean DOC 8.5 years Treatment duration: 2 weeks; follow-up: 3 months
Outcomes	Functional status, morning stiffness, 15-meter walking time, hand grip strength, participant assessment of disease severity, joint tenderness, number of active joints and laboratory variables
Notes	Pre/post analysis, only point estimates presented 3 mild cases of side effects (thermal reaction) Supported in part by a grant from Mifal Hapayis Foundation in memory of Pinchas Sapir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes, patients?	Unclear risk	Control participants were aware of the other treatments, so no blinding of participants

Sukenik 1990b (Continued)

Blinding of participants and personnel (performance bias) All outcomes, care providers?	Unclear risk	No information on blinding of care providers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessment blinded, but not for participant-assessed outcomes
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Unclear risk	No mention of dropouts; seems to be an available case analysis
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Unclear risk	Unclear whether intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Compliance was unclear
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

Sukenik 1995

Methods	RCT Blinding: observer
Participants	Outpatient clinic Soroka, Israel; n = 36 RA as defined by ARA
Interventions	I: baths in Dead Sea, n = 9; 11% male; mean age 61.6 years; mean DOC 10.9 years C1: sulphur baths, n = 9; 11% male; mean age 57.8 years; mean DOC 15.1 years C2: Dead Sea baths + sulphur baths, n = 10; 20% male; mean age 58.3 years; mean DOC 18.5 years C3: no-treatment control, n = 8; 12% male; mean age 62.4 years; mean DOC 11.3 years Treatment duration: 2 weeks; follow-up: 3 months
Outcomes	Functional status, morning stiffness, 15-meter walking time, hand grip strength, participant assessment of disease severity, joint tenderness and number of active joints
Notes	Pre/post analysis, only point estimates presented Supported by a grant from the Chief Scientist, Ministry of Health, Jerusalem

Risk of bias
Balneotherapy (or spa therapy) for rheumatoid arthritis (Review)

Sukenik 1995 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes, patients?	Unclear risk	Control participants were aware of the other treatments, so no blinding of participants
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Unclear risk	No information on blinding of care providers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessment was blinded, but not for participant-assessed outcomes
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Unclear risk	No mention of dropouts, seems to be an available case analysis
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Unclear risk	Unclear whether intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Compliance was unclear
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

Yurtkuran 1999

Methods	RCT Blinding: observer
Participants	Outpatient clinic Bursa, Turkey; n = 57 RA as defined by ARA
Interventions	I: mineral baths, n = 32; 19% male; mean age 44 years; mean DOC 15.5 years

Yurtkuran 1999 (Continued)

C: drug (Cyclosporin A; 3.5 mg/kg) treatment, n = 25; 16% male; mean age 39 years; mean DOC 12 years
Treatment duration: I: 3 weeks; C: 2 months

Outcomes	Pain (VAS), grip strength, global evaluation (improvement), laboratory variables
Notes	Pre/post analysis; measures of variability are unclear (SEM or SD) No information on funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes, patients?	Unclear risk	No information on blinding of participants or caregivers
Blinding of participants and personnel (performance bias) All outcomes, care providers?	Unclear risk	No information on blinding of participants or caregivers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Observer was blinded, not for participant-assessed outcomes
Incomplete outcome data (attrition bias) All outcomes, drop-outs?	Unclear risk	No information on dropouts
Incomplete outcome data (attrition bias) All outcomes, ITT analysis?	Unclear risk	Unclear whether intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Unclear
Similarity at baseline	Low risk	Groups were comparable at baseline
Co-interventions avoided	Unclear risk	Unclear whether co-interventions were avoided
Compliance acceptable	Unclear risk	Compliance was unclear
Timing outcome assessment comparable	Low risk	Timing of outcome measures was comparable

AIMS = arthritis impact measurement scales; ARA = American Rheumatism Association; DOC = duration of compliance; RCT = randomised controlled trial; ROM = range of motion; SD = standard deviation; SEM = standard error of means.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Annegret 2013	Just 3 patients with RA were included
Baldwin 1972	Not an RCT
Buskila 2001	No patients with RA were included
Danneskiold-S 1987	Not an RCT
Elkayam 2000	No patients with RA were included
Estefan 1999	Letter to the editor
Fioravanti 2000	No patients with RA were included
Forestier 1970	Not an RCT
Gambichler 2001	No patients with RA were included
Green 1993	No patients with RA were included
Guillemin 2001	Not an RCT; no patients with RA were included
Halevy 2001	No patients with RA were included
Hill 1999	Not an RCT; no patients with RA were included
Klemm 1971	Outcome measures were inappropriate
Landewe 1992	Not an RCT
Neumann 2001	No patients with RA were included
Nguyen 1997	No patients with RA were included
Nicholls 1990	No patients with RA were included
Rijswijk 1992	Not an RCT
Steiner 1979	Not an RCT
Strauss-Blasche 2000	Not an RCT; no patients with RA were included
Sukenik 1994	Not an RCT
Sukenik 2001	Not an RCT; no patients with RA were included
Svarcova 1990	Not an RCT
Sylvester 1990	No patients with RA were included
Szucz 1989	Not an RCT

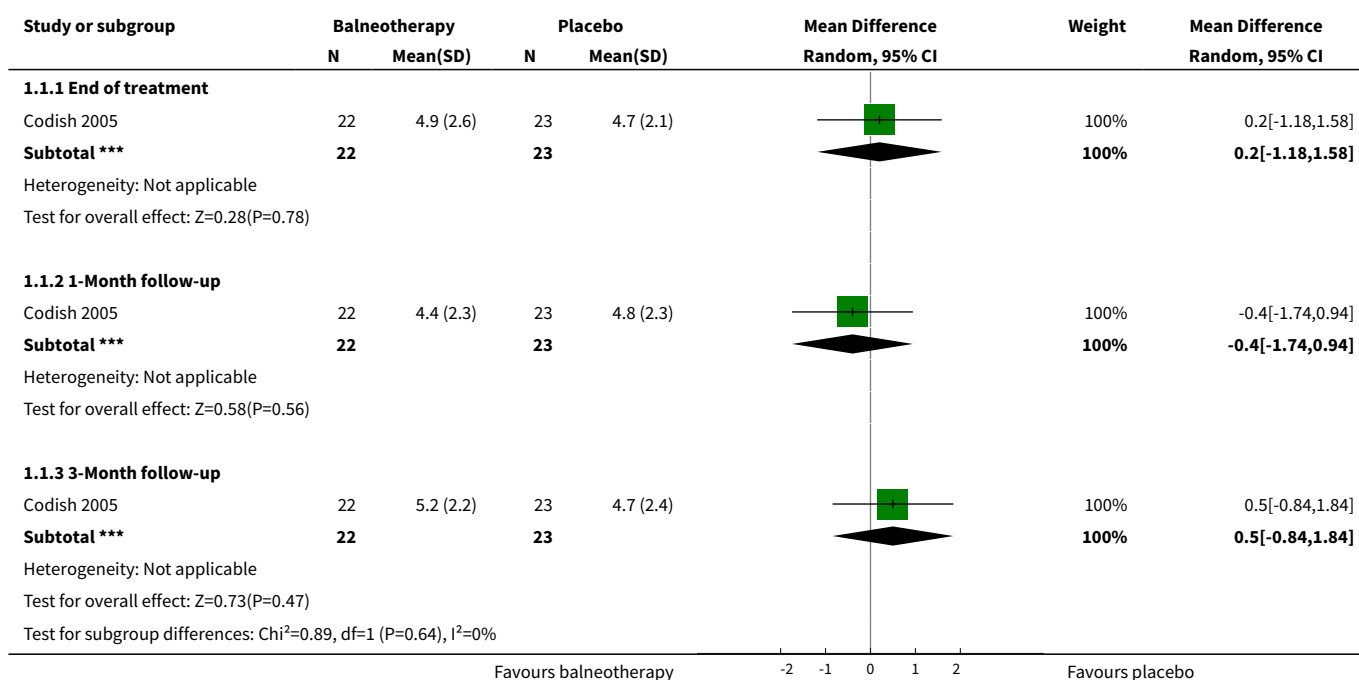
Study	Reason for exclusion
van Tubbergen 2001	No patients with RA were included
Wigler 1996	No patients with RA were included
Youn 1998	Not an RCT; no patients with RA were included
Özcelik 2000	Not an RCT; no patients with RA were included

DATA AND ANALYSES

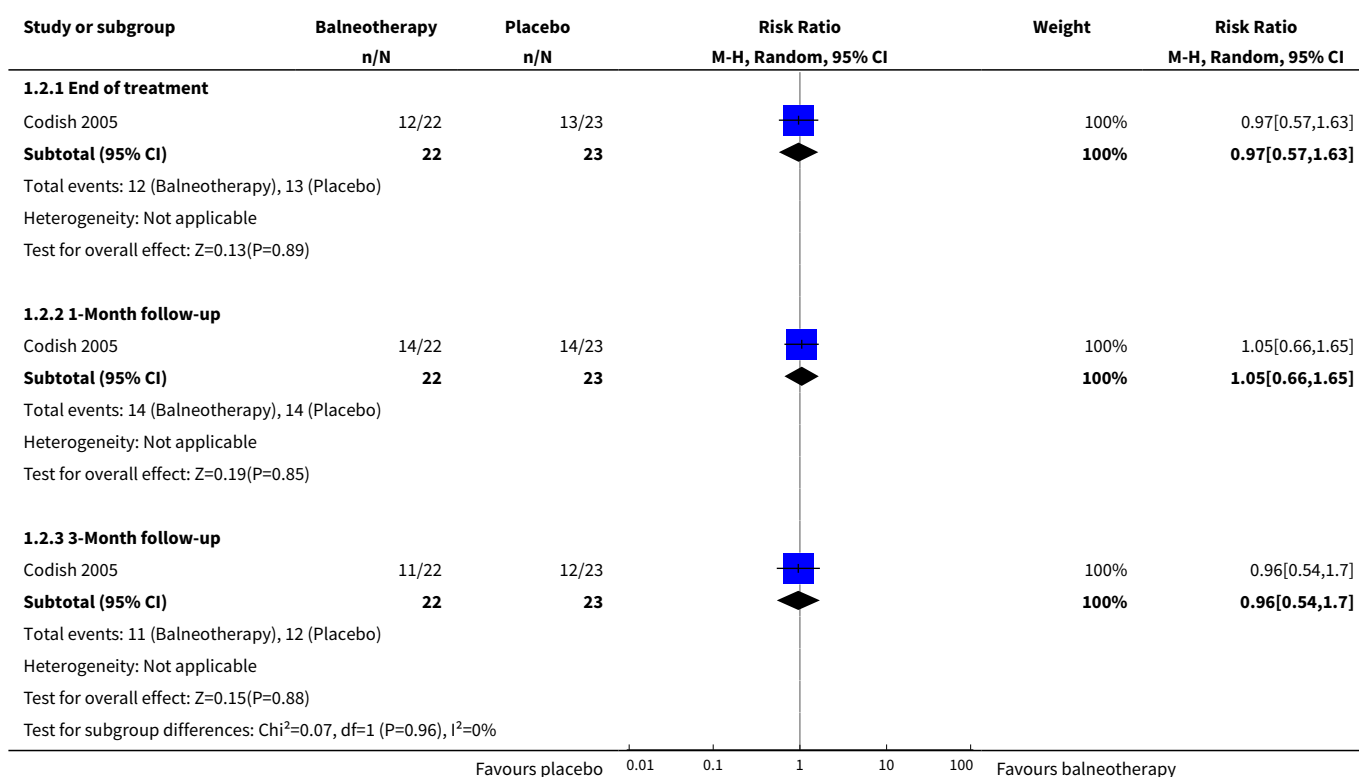
Comparison 1. Balneotherapy versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 End of treatment	1	45	Mean Difference (IV, Random, 95% CI)	0.20 [-1.18, 1.58]
1.2 1-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.74, 0.94]
1.3 3-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	0.5 [-0.84, 1.84]
2 Improvement	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 End of treatment	1	45	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.57, 1.63]
2.2 1-Month follow-up	1	45	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.66, 1.65]
2.3 3-Month follow-up	1	45	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.54, 1.70]
3 Tender joints	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 End of treatment	1	45	Mean Difference (IV, Random, 95% CI)	-6.0 [-9.57, -2.43]
3.2 1-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	-5.1 [-8.58, -1.62]
3.3 3-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	-4.60 [-8.72, -0.48]
4 Swollen joints	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 End of treatment	1	45	Mean Difference (IV, Random, 95% CI)	0.10 [-1.58, 1.78]
4.2 1-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	0.10 [-1.45, 1.65]
4.3 3-Month follow-up	1	45	Mean Difference (IV, Random, 95% CI)	0.60 [-0.90, 2.10]

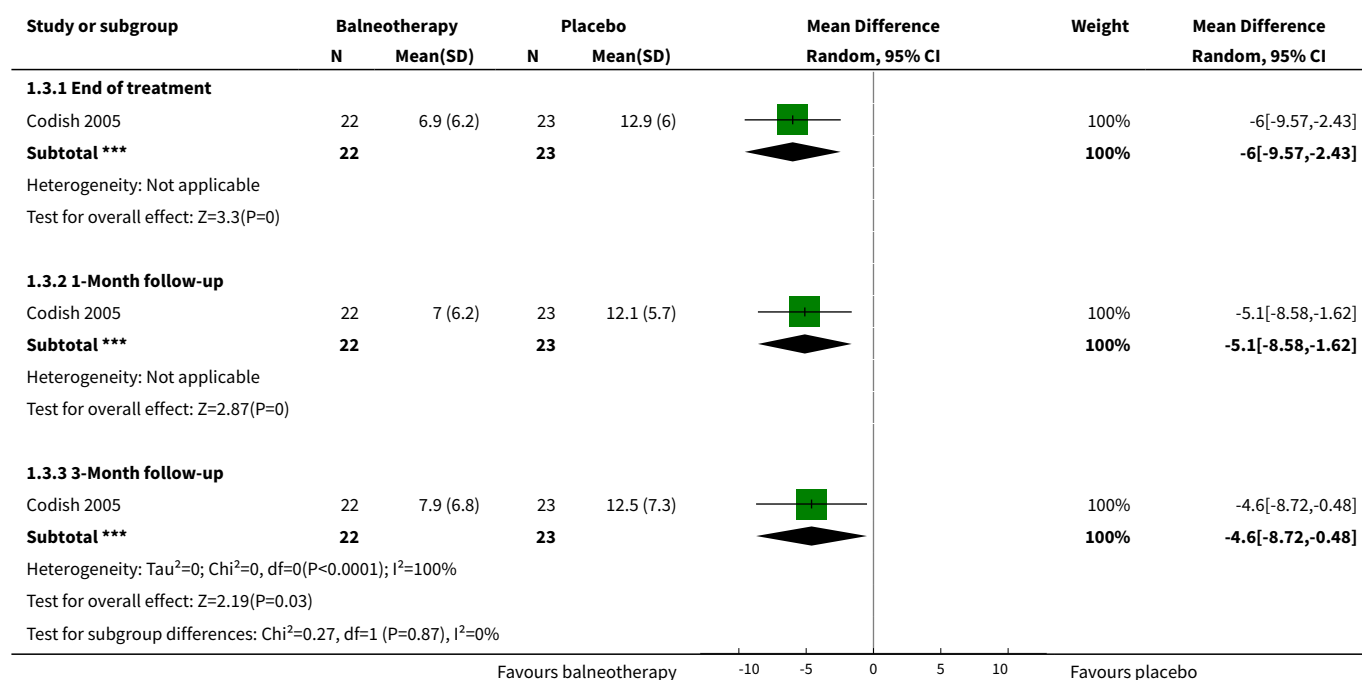
Analysis 1.1. Comparison 1 Balneotherapy versus placebo or no treatment, Outcome 1 Pain intensity.



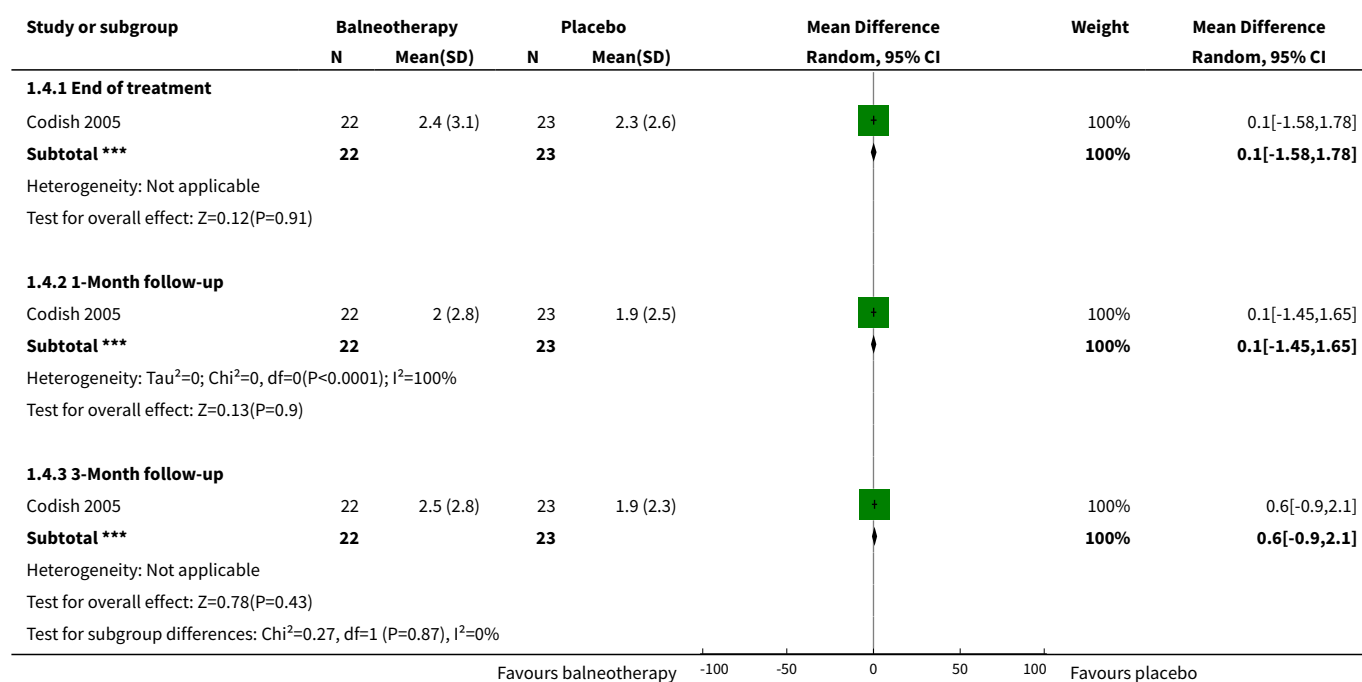
Analysis 1.2. Comparison 1 Balneotherapy versus placebo or no treatment, Outcome 2 Improvement.



Analysis 1.3. Comparison 1 Balneotherapy versus placebo or no treatment, Outcome 3 Tender joints.



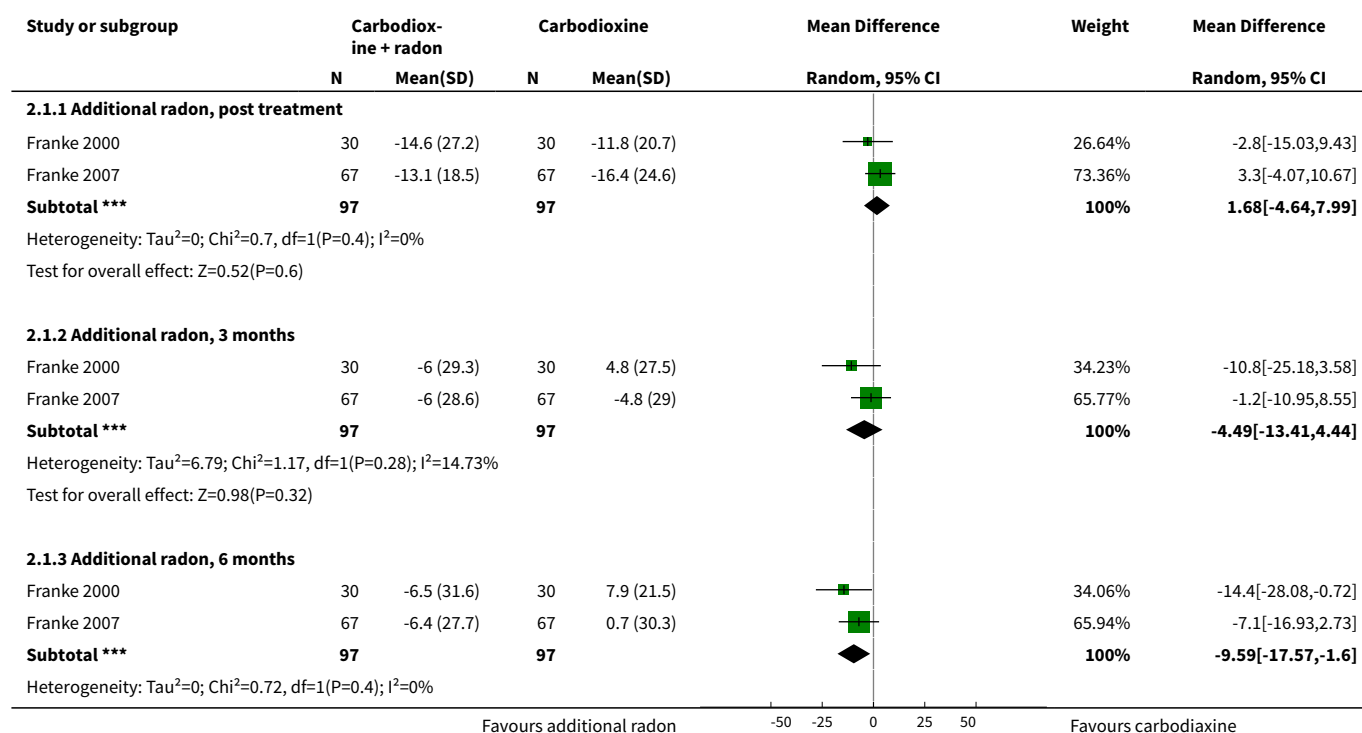
Analysis 1.4. Comparison 1 Balneotherapy versus placebo or no treatment, Outcome 4 Swollen joints.

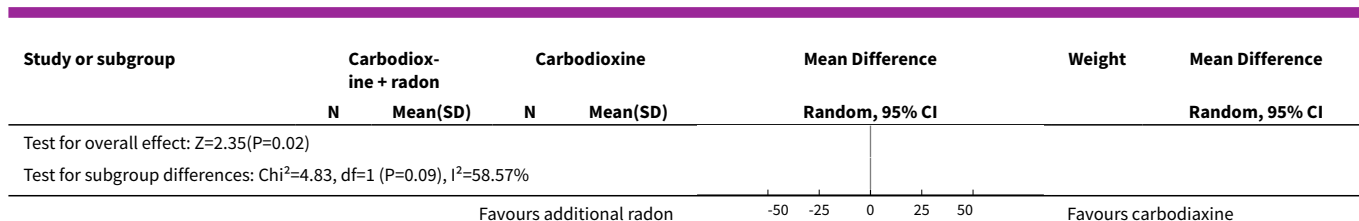


Comparison 2. Additional radon in carbon dioxide versus carbon dioxide alone

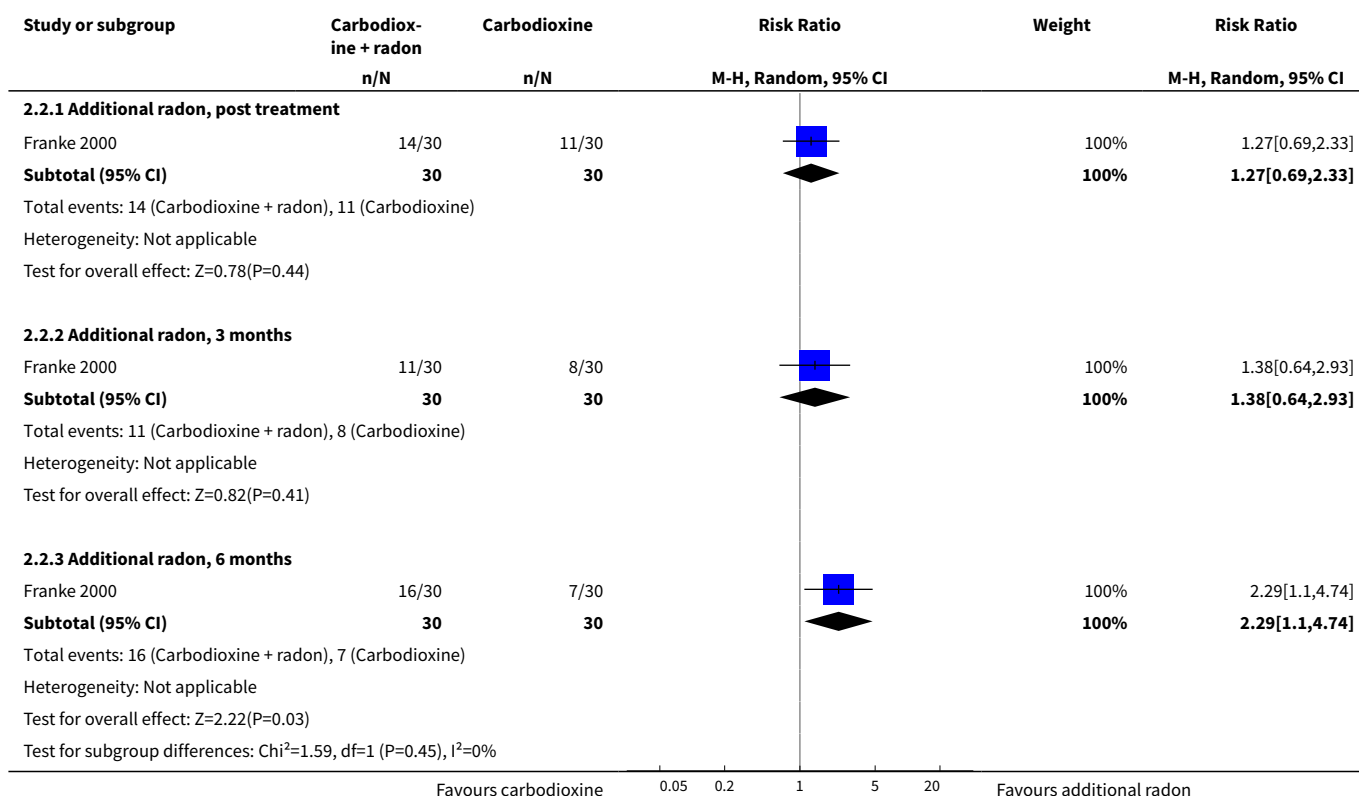
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain intensity	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Additional radon, post treatment	2	194	Mean Difference (IV, Random, 95% CI)	1.68 [-4.64, 7.99]
1.2 Additional radon, 3 months	2	194	Mean Difference (IV, Random, 95% CI)	-4.49 [-13.41, 4.44]
1.3 Additional radon, 6 months	2	194	Mean Difference (IV, Random, 95% CI)	-9.59 [-17.57, -1.60]
2 Improvement	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Additional radon, post treatment	1	60	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.69, 2.33]
2.2 Additional radon, 3 months	1	60	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.64, 2.93]
2.3 Additional radon, 6 months	1	60	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.10, 4.74]

Analysis 2.1. Comparison 2 Additional radon in carbon dioxide versus carbon dioxide alone, Outcome 1 Pain intensity.





Analysis 2.2. Comparison 2 Additional radon in carbon dioxide versus carbon dioxide alone, Outcome 2 Improvement.

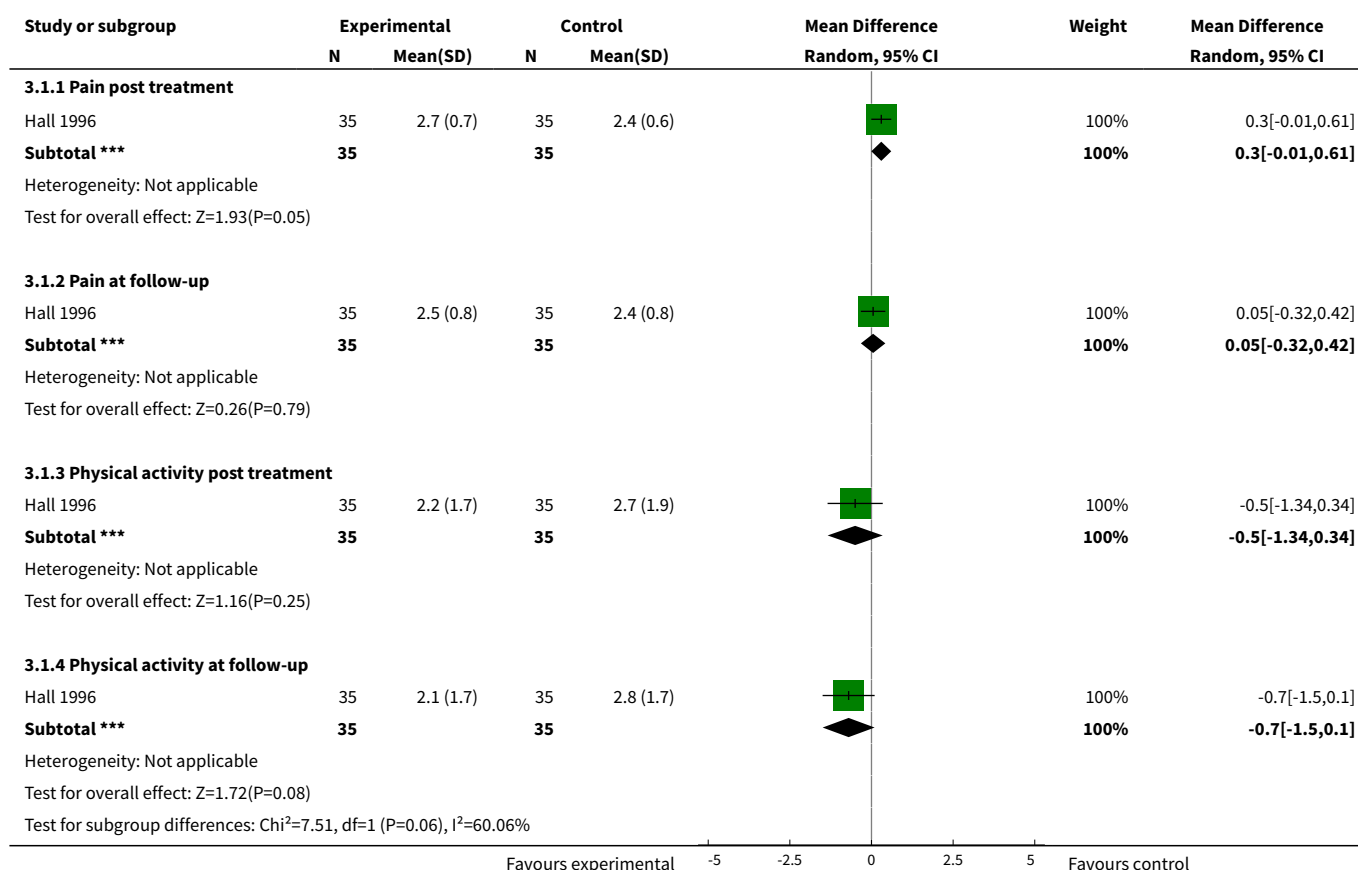


Comparison 3. Balneotherapy versus other treatments

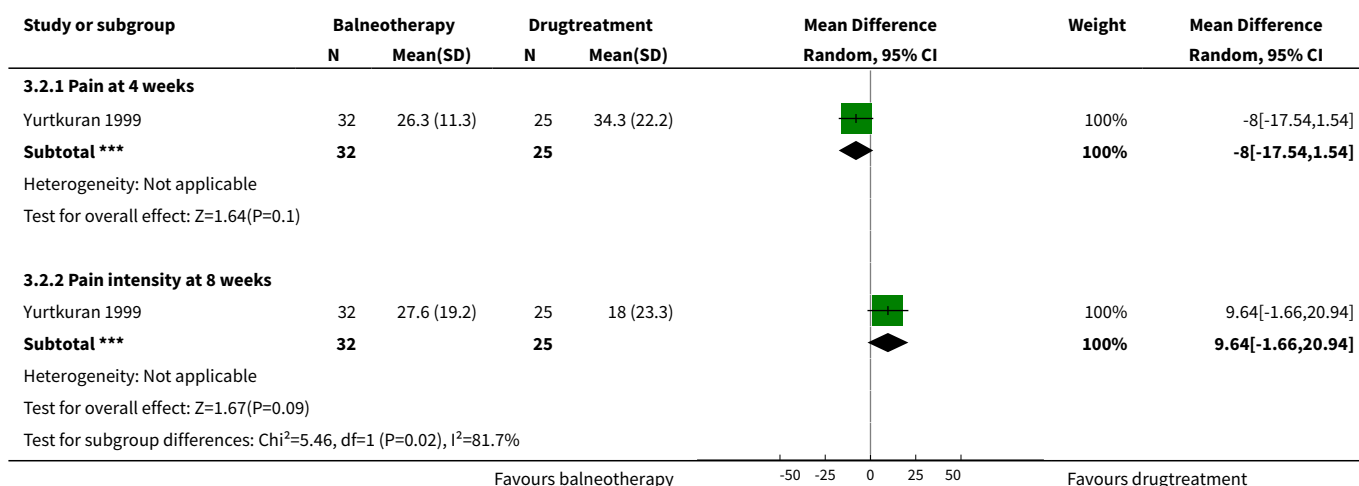
Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Versus relaxation	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Pain post treatment	1	70	Mean Difference (IV, Random, 95% CI)	0.30 [-0.01, 0.61]
1.2 Pain at follow-up	1	70	Mean Difference (IV, Random, 95% CI)	0.05 [-0.32, 0.42]
1.3 Physical activity post treatment	1	70	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.34, 0.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Physical activity at follow-up	1	70	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.50, 0.10]
2 Versus drug treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Pain at 4 weeks	1	57	Mean Difference (IV, Random, 95% CI)	-8.0 [-17.54, 1.54]
2.2 Pain intensity at 8 weeks	1	57	Mean Difference (IV, Random, 95% CI)	9.64 [-1.66, 20.94]
3 Versus drug treatment	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Improvement at 8 weeks	1	58	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.44, 3.83]
4 Versus drug treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Tender joints at 8 weeks	1	57	Mean Difference (IV, Random, 95% CI)	8.9 [3.83, 13.97]
4.2 Swollen joints at 8 weeks	1	57	Mean Difference (IV, Random, 95% CI)	1.5 [-1.25, 4.25]

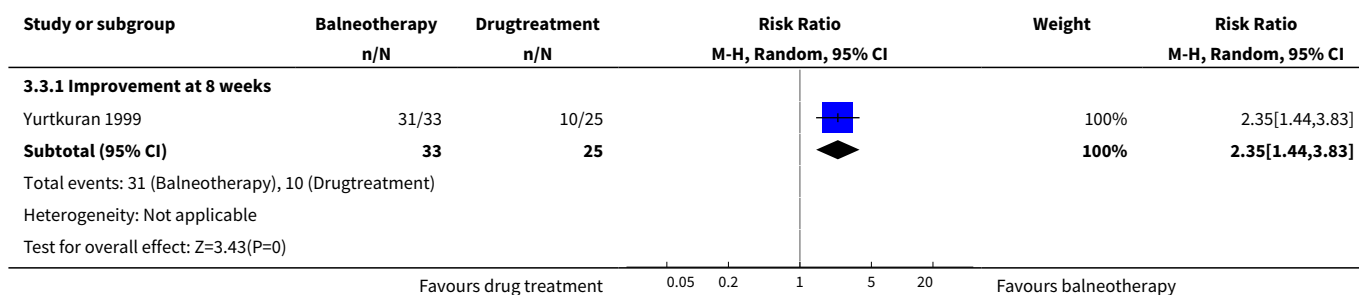
Analysis 3.1. Comparison 3 Balneotherapy versus other treatments, Outcome 1 Versus relaxation.



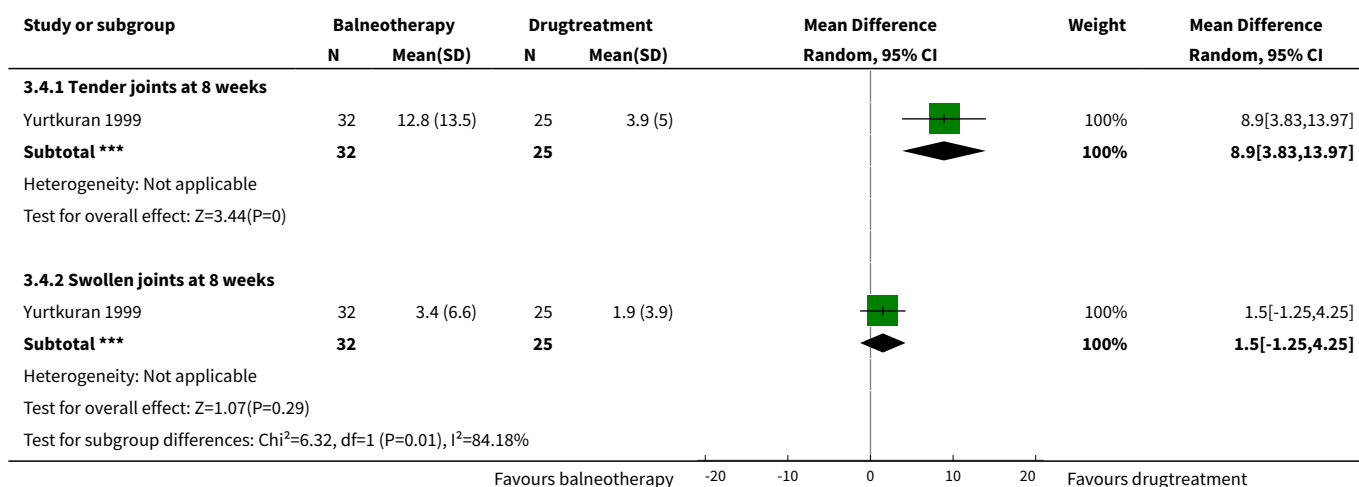
Analysis 3.2. Comparison 3 Balneotherapy versus other treatments, Outcome 2 Versus drug treatment.



Analysis 3.3. Comparison 3 Balneotherapy versus other treatments, Outcome 3 Versus drug treatment.



Analysis 3.4. Comparison 3 Balneotherapy versus other treatments, Outcome 4 Versus drug treatment.



APPENDICES

Appendix 1. MEDLINE search strategy

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\$ or reumat\$ or revmarthrit\$) adj3 (arthrit\$ or artrit\$ or diseas\$ or condition\$ or nodule\$)).tw.
3. (felty\$ adj2 syndrome).tw.
4. (caplan\$ adj2 syndrome).tw.
5. (sjogren\$ adj2 syndrome).tw.
6. (sicca adj2 syndrome).tw.
7. still\$ disease.tw.
8. bechterew\$ disease.tw.
9. or/1-8
10. exp Balneology/
11. balneo\$.tw.
12. Ammotherap\$.tw.
13. (bath or baths or bathe\$ or bathing).tw.
14. Hydrotherapy/
15. hydrotherap\$.tw.
16. Climatotherapy/
17. climatotherap\$.tw.
18. thalassotherap\$.tw.
19. (water or aqua\$ or climate or mud or spa).tw.
20. or/10-19
21. 9 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. drug therapy.fs.
27. randomly.ab.
28. trial.ab.
29. groups.ab.
30. or/22-29
31. (animals not (humans and animals)).sh.

32. 30 not 31

33. 21 and 32

1. ((exp osteoarthritis OR osteoarthr\$.tw. OR (degenerative adj2 arthritis).tw. OR arthrosis.tw.) OR (exp arthritis, rheumatoid/ OR ((rheumatoid OR reumatoid OR revmatoid OR rheumatic OR reumatic OR revmatic OR rheumat\$ OR reumat\$ OR revmarthrit\$) adj3 (arthrit\$ OR artrit\$ OR diseas\$ OR condition\$ OR nodule\$)).tw. OR (felty\$ adj2 syndrome).tw. OR (caplan\$ adj2 syndrome).tw. OR (sjogren\$ adj2 syndrome).tw. OR (sicca adj2 syndrome).tw. OR still\$ disease.tw. OR bechterew\$ disease.tw.))

2. (exp Balneology OR balneo\$.tw. OR Ammotherap\$.tw. OR (bath OR baths OR bathe\$ OR bathing).tw. OR Hydrotherapy/ OR hydrotherap\$.tw. OR Climatotherapy/ OR climatotherap\$.tw. OR thalassotherap\$.tw. OR (water OR aqua\$ OR climate OR mud\$ OR spa).tw.)

3. (randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) NOT (animals not (humans and animals)).sh.

4. #1 AND #2 AND #3

PubMed:

1. ((osteoarthritis[mesh] OR osteoarthr*[tw] OR (degenerative arthritis)[tw] OR arthrosis[tw]) OR (rheumatoid arthritis[mesh] OR ((rheumatoid OR reumatoid OR rheumatic OR reumatic OR rheumat* OR reumat*) AND (arthrit* OR artrit* OR diseas* OR condition* OR nodule*))[tw] OR (felty* syndrome)[tw] OR (caplan* syndrome)[tw] OR (sjogren* syndrome)[tw] OR (sicca syndrome)[tw] OR still* disease[tw] OR bechterew* disease[tw]))

2. (Balneology[mesh] OR balneo*[tw] OR Ammotherap*[tw] OR (bath OR baths OR bathe* OR bathing)[tw] OR Hydrotherapy[mesh] OR hydrotherap*[tw] OR Climatotherapy[mesh] OR climatotherap*[tw] OR thalassotherap*[tw] OR (water OR aqua* OR climate OR mud* OR spa)[tw])

3. (randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo[tiab] OR clinical trials as topic[mesh] OR trial*[ti]) NOT (animals[mesh] NOT humans[mesh])

4. #1 AND #2 AND #3

FEEDBACK

Points to consider when interpreting the results and conclusions of this review, 12 April 2017

Summary

We read with great interest the Cochrane review on balneotherapy (or spa therapy) for rheumatoid arthritis by Verhagen et al. [1]. However, we would like to address the points below that should be considered when interpreting the results and conclusions of this review.

1) The review authors considered the intervention of control group as a placebo in a trial included in the review, which tested mud compress therapy for the hands of rheumatoid arthritis patients [2]. However, the intervention of control group in that study was heated attenuated mud compress not a placebo [2]. Indeed, that study aimed to investigate whether mineral content of mud would have any additional benefit in the heated mud compress therapy. In other words, the control group received 'heated' attenuated mud compress; and since that therapy had thermal effect, categorizing that control therapy as a placebo was inappropriate. Therefore, the results and conclusions regarding the "balneotherapy versus placebo or no treatment" should be interpreted with caution. Nevertheless, this inappropriate reporting may be originated from lack of knowledge of basic characteristics of balneological interventions, which include balneotherapy (mineral water immersion), peloidotherapy/mud therapy (medical peloid or mud applications), hydropinotherapy (mineral water drinking), inhalation therapy (mineral water inhalation) and hydrotherapy (tap water immersion and exercise), if not from lack of caution to distinguish active from inactive control intervention. Furthermore, the results of the review do not match those from the original study in terms of response rate (improvement). The original paper reported statistically significant differences (please see Table 4 in original study) [2]; however, the review authors' analysis revealed no significant differences. We believe that this discrepancy should have mentioned and explained in the review and needs clarification.

2) The review authors wrongly defined one of the investigated interventions of a study as balneotherapy. However, the tested intervention in reality was hydrotherapy since tap water was used not mineral water [3]. In fact, that study aimed to investigate whether hydrotherapy in form of aquatic exercise would result in a greater therapeutic benefit than hydrotherapy in form of seated passive immersion, land exercise or progressive relaxation [3]. Therefore, classification of that intervention as balneotherapy was ill-chosen since the water used was not a mineral water. We think that this inaccurate classification additionally must have contributed the heterogeneity of the balneotherapy interventions observed in the review. Thereby, the results and conclusions regarding the "balneotherapy versus other

treatments” should be interpreted with caution. Nevertheless, this approach is not well-structured definition, and once again, may indicate lack of interpretation of even the basic characteristics and application modes of balneological interventions. (see above).

3) The conclusions of the review authors on two radon therapy studies [4, 5] should also be read with caution: “adding radon to carbon dioxide baths did not improve pain intensity at three months but may improve overall well-being and pain at six months compared with carbon dioxide baths without radon, but this may have happened by chance.” However, they failed to explain why the results of these two studies with low risk of bias might have happened by chance. The review authors should have explained the scientific rationale and evidence for attributing the differences to the chance. On the other hand, the radon studies by Franke and colleagues are spa therapy trials, in which both groups stayed in a spa resort and received balneotherapy (either baths with natural mineral water rich in radon and carbondioxide or artificially produced carbondioxide baths of the same carbondioxide concentration to maintain the blinding of patients and to investigate specific effects of radon), diseases-specific exercises, physiotherapy, massage therapy, hydrogalvanic baths and were offered occupational therapy, leisure time sports and relaxation therapy [4, 5]. In other words, the groups have undertaken the same package of multiple interventions plus balneotherapy (radon+carbondioxide or only carbondioxide); this may explain why the expected effect size would be small which was correctly reported in those two studies.

4) The review authors wrongly stated that information about adverse events was not reported in a radon spa therapy study [5] and a balneotherapy study [6], in plain language summary section. However, these studies have reported the adverse events. We believe that that information should be mentioned to provide more comprehensive information on harms of balneotherapy or spa therapy.

5) Due to concerns raised above, the results and conclusions of the Cochrane review on balneotherapy (or spa therapy) for rheumatoid arthritis may mislead the readers. The Cochrane Handbook states that review teams must include expertise in the topic area being reviewed [7]; accordingly we would suggest review teams should include expertise in the balneological interventions when further reviews on the safety and effectiveness of any balneological intervention will be being conducted, particularly for distinguishing active from inactive control intervention or hydrotherapy (tap water immersion) from balneotherapy (mineral water immersion), which were confused in this review.

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Reply

Thank you very much for your thorough reading of the review and your comments. We know that these comments come from people that are warm advocates of balneotherapy and we respect their opinion.

Question 1:

The comments concern here are the subgrouping used in our review, the definition of ‘balneotherapy’ and the results from the Codish study.

First, we had preplanned stratified analyses that included: a) versus no treatment or waiting list controls; b) versus other types of balneotherapy; and c) versus other treatment(s). We classified the study of Codish et al under a) as it compared mineral rich versus mineral depleted mudpacks. The latter we considered a placebo as the authors described that they did their best to make both interventions look like the same (The appearance, size, weight, and texture of both compress types were identical), but we agree that that was our own decision. I agree with Mr Karagulle that the using the term ‘placebo’ might not be correct for the intervention in the control group. Nevertheless, we do think this study is in the correct subgroup. Only the wording would change, not the results.

Next Dr Karagulle states he is not happy with our definition of 'balneotherapy'. I know there is no universally accepted definition of balneotherapy and the one Dr Karagulle proposes is broader than the one we used. We followed an international consensus that declared: "One of the core elements of balneotherapy is the use of (natural) mineral waters, gases and peloids (including packs = local application of peloids)". This is why we defined balneotherapy as follows: "Balneotherapy is defined as bathing in natural mineral or thermal waters (e.g. mineral baths, sulphur baths, Dead Sea baths), using mudpacks or doing both." Although our definition is less broad compared to the one proposed by Dr Karagulle, the fact remains that Codish et al evaluated the effectiveness of additional minerals in mudpacks, which methodological will always need to be categorized in the subgroup: versus no treatment or waiting list controls.

Lastly Dr Karagulle states that Codish et al found statistical significant differences in response rate as outcome. This is correct, but we used in our analysis the data under the para of 'patient global assessment'. This outcome measure is recommended as a core outcome in many studies, so future trials can add to this outcome. The response rate in Codish et al is a difficult rating system, including the physician rating. We consider this responder definition unique (definitely not corresponding to the recommended definition by the OARSI) and incorrect. Therefore we refrained from using this outcome.

Question 2:

Here the comments concern the inclusion of a study that, according to Dr Karagulle, should not be included. I know that the aim of the study of Hall et al was to evaluate the effectiveness of hydrotherapy, which we did not consider balneotherapy. Nevertheless one of the original control arms of Hall et al fell within our definition of balneotherapy, namely: "bathing in mineral or thermal waters" (seated immersion). This (control) intervention arm became therefore our intervention under study.

Inclusion of this study was, nevertheless, under heavy debate within our group, so I can understand the comments of Dr Karagulle et al. Nevertheless, our conclusion about the heterogeneity of balneotherapy interventions concerned all included studies, excluding this one would not change our conclusion.

Question 3

This comment addresses the statement of us: "this may have happened by chance", and the difference in interventions in both studies of Franke et al.

First, we made this statement "by chance", only in the plain language section as we needed to reflect the fact that these results are not very firm. We are willing to choose another formulation next update.

Second, indeed the patients in the studies of Franke et al received a multimodal treatment package, with the only difference between groups was the addition of radon. Therefore this radon can be held responsible for the treatment differences, exactly what the authors state they would like to know. The small effect sizes are therefore not due to the multimodal treatment package as everyone received it.

Question 4

Dr Karagulle is right, we meant to state in the plain language summary that there were no side effects reported in the study of Franke 2007, not that the information about side effects was lacking, as the authors indeed stated there were no side effects. We have adjusted the text in the plain language summary.

Question 5

We respectfully disagree with dr Karagulle, I do not think that our conclusions are unjustified and may mislead the reader. We also included two experts in the topic area: J Lambeck and J Cardoso, so I think we followed the Cochrane handbook.

Nevertheless, the biggest challenge in this area is that we need large studies with low risk of bias, and we hope and encourage Dr Karagulle and his team to fill this gap of knowledge.

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WHAT'S NEW

Date	Event	Description
23 June 2017	Feedback has been incorporated	Feedback incorporated; minor correction in the plain language summary

HISTORY

Review first published: Issue 3, 1999

Date	Event	Description
30 December 2014	New citation required but conclusions have not changed	Updated the methods
30 December 2014	New search has been performed	Conducted new search yielding 2 new included studies
21 May 2008	Amended	Converted to new review format. CMSG ID C010-R
23 August 2007	New search has been performed	In this update, we included 1 extra study comparing mineral baths with drug treatment (Cyclosporin A). The study consisted of 57 participants and reported that mineral baths were more beneficial. The strength of the evidence identified in this systematic review remains limited
28 August 2003	New citation required and conclusions have changed	Substantive amendments made

CONTRIBUTIONS OF AUTHORS

Arianne P Verhagen (APV) and Henrica CW de Vet (HCWdV) initiated the review; APV wrote the first draft of the review. APV developed the search strategy, and APV and Sita MA Bierma-Zeinstra (SMAB-Z) performed study selection and analysis and wrote the review. Rob A de Bie (RAdB) and HCWdV performed the quality assessment, and Jefferson R Cardoso (JRC) and APV performed data extraction. In this update, Johan Lambeck (JL) helped with the search for and selection of studies.

SMAB-Z, RAdB, JRC, Maarten Boers (MB) and HCWdV all critically reviewed successive drafts of the review. APV served as the guarantor of the review.

DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None known.

INDEX TERMS

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*Balneology; *Hydrotherapy; Antirheumatic Agents [therapeutic use]; Arthritis, Rheumatoid [*therapy]; Cyclosporine [therapeutic use]; Mud Therapy; Osteoarthritis [*therapy]; Pain Management [methods]; Publication Bias; Radon [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans